BISOPROLOL 5 MG TABLETS

BISOPROLOL 10 MG TABLETS

PL 15582/0023-4

UKPAR

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BISOPROLOL 5 MG AND 10 MG TABLETS

PL 15582/0023-4

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Zanza Healthcare Limited a Marketing Authorisation (licence) for the medicinal products Bisoprolol 5mg and 10mg Tablets (PL 15582/0023-4). This medicine is available by prescription only.

Bisoprolol is known as a beta blocker and is used to treat high blood pressure or angina (chest pain). Beta blockers work by blocking messages to the beta receptors of the heart, which slows heart activity. The decrease in heart activity has the effect of decreasing blood pressure and also making an attack of angina less likely.

Bisoprolol 5mg and 10mg Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

BISOPROLOL 5 MG AND 10 MG TABLETS

PL 15582/0023-4

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Bisoprolol 5mg and 10mg Tablets to Zanza Healthcare Limited on 24 August 2006. These are prescription-only medicines.

These are national applications for Bisoprolol 5mg and 10mg Tablets submitted under Article 4.8(a)(iii) of Directive 2001/83, claiming essential similarity to Emcor 5mg and 10mg tablets (PL 00493/0126-7) licensed in the UK on the 11 February 1988 to E Merck Limited.

Bisoprolol is a beta-1 cardioselective adrenergic blocking agent intended for treatment of hypertension and angina.

PHARMACEUTICAL ASSESSMENT

I. REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

A certified translation of the finished product manufacturer's manufacturing licence has been provided and includes approval for manufacture of tablets. The date on the licence is September 2002.

II. INTRODUCTION

These are national abridged applications submitted under article 4.8(a)(iii) of Directive 2001/83, claiming essential similarity to Emcor 5mg and 10mg tablets (E Merck Limited). Emcor (PL 00493/0126-7) was approved in the UK on 11 February 1988 as a joint development with Monocor (Cyanamid, PL 00095/0177-8, approved 18 December 1987).

Bisoprolol is a beta-1 selective adrenergic blocking agent intended for treatment of hypertension and angina. The approved daily dosage for the reference product is in the range 5 to 20mg daily.

III. DRUG SUBSTANCE

The manufacturer of bisoprolol hemifumarate is in possession of a drug master file. A letter authorising access to the confidential data within this file has been provided. This drug master file has been previously assessed in this Agency in relation to other applications for oral tablets.

The DMF is dated December 2000 and the method of synthesis is the same as that previously assessed.

A re-test period of 2 years has been assigned to the active ingredient. Results generated from up to 48 months' storage confirm the suitability of the retest interval.

IV. DRUG PRODUCT

IV.1 Description and qualitative composition of the drug product

Ingredient	**Function**	**Reference Standard**
Bisoprolol hemifumarate	Active Substance	HSE
Excipients		
Maize Starch	Binder/disintegrant	Ph. Eur
Microcrystalline cellulose	Diluent and binder	Ph. Eur
Crospovidone	Disintegrant	Ph. Eur
Anhydrous calcium hydrogen phosphate	Binder	Ph. Eur
Magnesium stearate	Lubricant	Ph. Eur
Colloidal anhydrous silica	Flowing agent	Ph. Eur
Purified water	Solvent for granulation	Ph. Eur

Theoretical mass		
Film Coating		
Hypromellose	Film former	Ph. Eur
Titanium dioxide (E171)	Opacifier	Ph. Eur
Macrogol 6000	Plasticiser	Ph. Eur
Dimeticone 350	Antifoaming agent	Ph. Eur
Yellow iron oxide (E172)	Colouring agent	USP XXIII
Red iron oxide (E172)	Colouring agent	USP XXIII
Purified water	Solvent for coating	Ph. Eur

IV.2 Pharmaceutical Development

The products intended for marketing are presented as film-coated tablets. The 5mg tablets are ivory in colour and the 10mg tablets are light brown. Both tablets are scored on one side.

The composition of the tablet core is qualitatively similar to that of the brand leader product. All excipients are conventionally used in pharmaceutical products. The different strength tablets are produced to the same core mass by variation in the quantity of calcium phosphate filler.

The declared content of active ingredient is as the hemifumarate and this is acceptable, in view of the composition of the brand leader product.

The tablets are packed into PVdC coated PVC film blisters with aluminium foil backing.

The product used in the bioequivalence study is stated to have the same composition as that described for the commercial products.

Development studies focussed on achieving a formulation based on the composition of the brand leader and with appropriate physical properties for industrial manufacture. Results from formulation development studies have been provided.

Bisoprolol hemifumarate is soluble in water (1g in 10-30ml) and dissolution in water, 0.1M HCl and buffers at pH 4.75 and 7.2 is rapid and essentially complete in 10-20 minutes. The choice of conditions for routine control is acceptable. Dissolution profiles for the applicant's product and Emcor 5mg and 10mg are similar under these conditions.

Process development studies were conducted at a scale of 12,000 tablets (5mg) to define operating conditions for mixing, granulation and drying.

IV.3 Manufacture

Formulae for batch sizes of 1.25 million tablets of each strength are consistent with the declared composition of the commercial product. No active ingredient overage is employed.

A satisfactory flow diagram and description of the manufacturing process has been provided. Manufacture employs conventional pharmaceutical unit operations of mixing (granular and extragranular), granulation, drying, compression, film coating and packing. Manufacturing

equipment, operating conditions, in process controls and acceptance criteria have been defined and are acceptable.

Process validation studies have been conducted on pilot scale batches of 100,000 and 150,000 tablets for the 5mg and 10mg strengths, respectively. The results support the suitability and consistency of the method.

Confirmation has been provided that scale-up validation studies on the first three commercial batches will be conducted according to the same protocol and this is acceptable.

IV.4 Control of Excipients

Excipients comply with their individual monographs in Ph Eur with the exception of iron oxide (USP). In the absence of a Ph Eur monograph for the latter, this is acceptable. Certificates of analysis have been provided for excipients.

The stearic acid used to make the magnesium stearate has an EDQM TSE Certificate of Suitability (R1-CEP-2000-269 Rev 00), a copy of which has been provided.

IV.5 Control of Drug Product

Satisfactory control tests are applied at the time of release. Batch analytical results have been provided for two pilot batches (100-150,000 tablets) of each strength, manufactured at the site intended for commercial production. Results comply with the specification.

IV.7 Container Closure System

The manufacturer's technical information has been provided as justification for the primary container proposed. Confirmation of compliance of the primary PVC/PVdC film with the appropriate Ph Eur monographs has been provided. Testing is conducted on receipt by the product manufacturer is adequate and includes identity (IR) and other physical controls.

IV.8 Stability

Two pilot batches of each strength have been entered into stability studies under long-term, intermediate and accelerated conditions, in compliance with ICH recommendations. Tablets were tested for appearance, identification, disintegration, divisibility to assess the effect of storage on breaking the tablets along the score line, dissolution, related substances and assay.

Data up to 36 months have been provided for all batches stored at 25°C/60%RH, up to 12 months, for all batches stored at 30°C/60%RH and up to 6 months for all batches stored at 40°C/75%RH. Results are all within specifications for product stored at 25 and 30 ± 2°C. On the basis of these data, the applicant proposes a shelf-life of 36 months if stored at a temperature not exceeding 30°C.

Confirmation has been provided that three commercial batches of each strength will be entered into stability studies conducted under long-term and intermediate conditions and that details of any significant out of specification results will be provided.

V. APPENDICES

V.1 Facilities and Equipment - Not applicable.

V.2 Adventitious Agents Safety Evaluation

Magnesium stearate is of animal origin and its suitability for use in medicinal products is supported by an EDQM TSE Certificate of Suitability from the supplier intended for the commercial product. This is satisfactory.

V.3 Novel Excipients – Not applicable

VI. REGIONAL INFORMATION

VII. ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

These are all acceptable.

VII.1 Other information

VII.1.1 Bioavailability, bioequivalence

An open, randomised, three way cross-over biostudy was carried out on 27 (25 completed) healthy male and female volunteers to compare the bioavailability of the applicant's bisoprolol tablets to that of Emcor 10mg tablets, sourced from the UK market.

The study consisted of three treatment phases with a wash out period of 7 to 14 days. A single 10mg dose (one 10mg tablet, or two 5mg tablets) was given in each arm of the study.

Plasma samples were analysed by validated HPLC with detection by fluorimetry with a linear range of 0.88-115.0 ng/ml.

Results were analysed using ANOVA and the mean pharmacokinetic parameters are tabulated below:

	Bisoprolol 5mg (Test)	**Bisoprolol 10mg (Test)**	**Emcor (Reference)**
C_{max} (ng/ml)	51.4 ± 6.21	54.7 ± 9.41	52.0 ± 7.69
T_{max} (h)	2.12 ± 0.92	1.76 ± 0.89	1.76 ± 0.83
AUC_{0-t} (ng.h/ml)	672 ± 99.1	669 ± 95.5	666 ± 118
$AUC_{0-\infty}$ (ng.h/ml)	694 ± 98.5	689 ± 96.2	686 ± 120

90% Confidence Interval	**Bisoprolol 10 vs Emcor**	**Bisoprolol 5 vs Emcor**
C_{max}	99.9-110.8	94.5-104.9
AUC_{0-t}	95.8-105.9	96.4-106.6
$AUC_{0-\infty}$	95.8-105.7	96.7-106.7

The 90% confidence intervals for AUC are within the guideline limits of 80-125%. The applicant's tablets can, therefore, be considered to be bioequivalent to Emcor, the UK brand leader.

VII.1.2 Essential similarity

The applicant's products contain the same qualitative composition in terms of active ingredients and are the same dosage form as the UK brand leader product. Bioequivalence has been demonstrated between 1 x 10mg and 2 x 5mg bisoprolol tablets manufactured by Rottendorf and Emcor 10mg from the UK market. The applicant's claims for essential similarity are justified.

VIII ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

Marketing authorisations may be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none is required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION

These are two, abridged standard, non-committee, national applications for generic Bisoprolol of two strengths (5 and 10mg) claiming essential similarity to Emcor (& Emcor LS), the UK brand leader product (E Merck Limited, PL 00493/0126-7). The applicant does not propose to initiate a mutual recognition procedure in the event of a positive opinion.

GCP aspects

There are no GCP issues

Therapeutic Class

Cardioselective betablocker
ATC Code: C07B b07

Background

Of the Active: Bisoprolol is a potent cardioselective B1 receptor blocking agent devoid of intrinsic sympathomimetic activity. The active has been well established in clinical use since 1988 in the treatment of hypertension and angina. Recently, bisoprolol has also received authorisation in the treatment of heart failure, following completion and publication of the CIBIS II trial.

Of the Application: The application is based on essential similarity to the brand leader and the criteria for exemption are satisfied. The applicant has provided the appropriate bioequivalence study that is discussed in the appropriate section of this report.

Regulatory Status

This is the first MAA for this product in the EU or outside of EEA.

Indications, Dose and Dose Regimen

As proposed in SPC, these are identical to the reference product. They include treatment of hypertension and angina pectoris. Dose and dose regimen are identical to the reference product SPC; 5-10 mg daily with a maximum of 20mg in hypertension. These are satisfactory.

Consideration for Paediatric use

The current product has no paediatric development programme and bisoprolol is not recommended for use in children, due to lack of sufficient experience.

Assessor's Comment

The basis of the application, the indications and posology are appropriate and acceptable. The absence of a paediatric development programme is not considered a major drawback in this situation, as there is no urgent need for use of this drug in paediatric practice.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Pharmacodynamics

Summary & Overall conclusion:

The pharmacology of bisoprolol is well documented and well known. No unusual characteristics have been demonstrated. Therefore, so long as the indications, the warnings and contraindications are followed as per the SPC, clinical use of this active should be with a favourable benefit:risk ratio. The bioequivalence of the current generic product with the reference product is discussed below.

Bioavailability & Bioequivalence

Bioequivalence study

The applicant has provided a three way bioequivalence study on 27 male and female healthy volunteers between 23 June 1999 and 29 July 1999. Subjects were 18-40 years old and 25 completed the study. Three products were compared in a three way cross-over, randomised study, with a washout period of 1-2 weeks.

Reference: Emcor 10mg Tablets (Merck KGaA, Germany & UK)
Test B: Bisoprolol-HCl-Rottendorf 10mg; Batch 1967305G
Test C: Bisoprolol-Rottendorf 5mg x2; Batch 1967311.

Results:

Parameter	Ref Prod (A)	Test –B (10mg)	Test-C; 5mg	90% CI A vs B	90% CI A vs C
Cmax (ng/ml)	52.0± 7.69	54.7 ± 9.41	51.4 ± 6.21	99.0-110.8	94.5-104.9
$AUC_{0\text{-}t}$ (ng*h/ml)	666 ± 118	669 ± 95.5	672 ±99.1	95.8-105.9	96.4-106.6
$AUC_{0\text{-}\infty}$ (ng*h/ml)	686 ±120	689 ± 96.2	964 ± 98.5	95.8-105.7	96.7- 106.7

Data are expressed as mean± SD, of geometric means.

Comments: The reference product chosen is appropriate and identical composition and dissolution profiles for reference products in the UK and France have been demonstrated as detailed in the expert report. The sampling times, study design and washout period are appropriate and acceptable. The 90% CI are within the set limits (CPMP NfG) and therefore it is considered that bioequivalence has been demonstrated.

CLINICAL EFFICACY

Summary

The efficacy of Bisoprolol in the indications sought have been well established since its first authorisation. The applicant has not provided any new studies or new data and this is acceptable for an application based on essential similarity.

CLINICAL SAFETY

Summary

Bisoprolol has been in clinical use since 1988 (first authorisation) and has not been the subject of a regulatory action. The indications sought are appropriate and identical to the

reference product. In this application based on essential similarity, the applicant has not provided any new data or new studies and no new indications are proposed. The safety of the active is therefore acceptable provided the product is used as proposed in the SPC.

CLINICAL EXPERT REPORT

An expert report from an appropriately qualified person has been provided. This is satisfactory.

PRODUCT LITERATURE

SPC: Summary of Product Characteristics

The proposed SPC is satisfactory.

PIL; Patient Information Leaflet

The PIL is satisfactory.

Labels and MAA

The labels and MAA form are considered satisfactory from a medical perspective.

CONCLUSIONS

Pharmacodynamics & Pharmacokinetics

The pharmacology of bisoprolol is well known and the documentation is considered satisfactory.

Bioequivalence

It is considered that adequate bioequivalence has been demonstrated based on the study details provided in the dossier.

Efficacy & Safety

The efficacy and safety of Bisoprolol are well known in the indications proposed and this is acceptable.

Risk – benefit

This is considered acceptable.

CLINICAL AND PRE-CLINICAL ASSESSORS' CONCLUSIONS

The Clinical assessor believes that grant of MA is acceptable.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Bisoprolol 5mg and 10mg 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.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Bisoprolol 5mg and 10mg Tablets. The risk benefit is therefore considered to be positive.

BISOPROLOL 5 MG AND 10 MG TABLETS

PL 15582/0023-4

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 1 July 2003
2	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 17 November 2003 and the quality dossier on 28 June 2004
3	The applicant responded to the MHRA's requests, providing further information on the clinical and quality dossiers on 23 November 2004 and 22 December 2004
4	Following assessment of the application the MHRA requested further information relating to the quality and clinical dossiers on 25 July 2005
5	The applicant responded to the MHRA's requests, providing further information on the quality dossier in November 2005
6	Following assessment of the response the MHRA requested further additional information relating to the quality dossier on 3 May 2006
7	The applicant responded to the MHRA's requests, providing further information on 7 June 2006
8	Following assessment of the response the MHRA requested further additional information relating to the clinical dossier on 25 July 2006
9	The applicant responded to the MHRA's requests, providing further information on 1 August 2006
10	The application was determined on 24 August 2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg bisoprolol fumarate (2:1)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Ivory coloured, scored, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Management of hypertension

2. Management of angina pectoris

4.2 Posology and method of administration

Adults: The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In some patients 5 mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver function, the dose should not exceed 10 mg bisoprolol once daily.

Elderly: No dosage adjustment is normally required, but 5 mg per day may be adequate in some patients; as for other adults, dosage may have to be reduced in cases of severe renal or hepatic dysfunction.

Children and adolescents under 18: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

Route of administration: Oral

4.3 Contraindications

Bisoprolol is contra-indicated in 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
- bradycardia (heart rate less than 60 beats/min prior to start of therapy)
- hypotension (systolic blood pressure < 100mmHg)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see Special Warnings and Precautions)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

4.4 Special warnings and precautions for use

Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases)
- concomitant treatment with inhalation anaesthetics (see Interactions section)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked
- strict fasting
- ongoing desensitisation therapy
- AV block of first degree
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints may occur particularly during the start of therapy)

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

- NYHA class II heart failure
- insulin dependent diabetes mellitus (type I)
- impaired renal function (serum creatinine ≥ 300 μmol/l)
- impaired liver function
- patients older than 80 years
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

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 $ß_2$-stimulants may have to be increased.

As with other ß-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 ß-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 thyrotoxicosis may be masked.

In patients with ischaemic heart disease, treatment should not be withdrawn abruptly.

Combination with calcium antagonists, clonidine or monoamine oxidase inhibitors (except MAO-B inhibitors) is not recommended. See 'Interactions' section.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

Calcium antagonists such as verapamil and to a lesser extent diltiazem: Negative influence on contractility, atrio-ventricular conduction and blood pressure. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Clonidine: Increased risk of "rebound hypertension" as well as exaggerated decrease in heart rate and cardiac conduction.

Monoamineoxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of ß-blockers but also risk of hypertensive crisis.

Combinations to be used with caution

Calcium antagonists such as dihydropyridine derivatives (eg, nifedipine): increased risk of hypotension. In patients with latent cardiac insufficiency, concomitant treatment with beta-blocking agents may lead to cardiac failure.

Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine): Effect on atrial conduction time may be potentiated and negative inotropic effect may be increased.

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrial conduction time may be potentiated.

Parasympathomimetic drugs (including tacrine): Atrio-ventricular conduction time may be increased.

Other ß-blockers, including eye drops, have additive effects.

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

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension. Continuation of ß-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving bisoprolol.

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

Prostaglandin synthetase inhibiting drugs: Decreased hypotensive effects.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

Sympathomimetic agents: Combination with bisoprolol may reduce the effect of both agents. Higher doses of epinephrine may be necessary for treatment of allergic reactions.

Tricyclic antidepressants, barbiturates, phenothiazines as well as other antihypertensive agents: Increased blood pressure lowering effect.

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.

Moxisylyte: Possibly causes severe postural hypertension.

Combinations to be considered

Mefloquine: increased risk of bradycardia

4.6 Pregnancy and lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, β-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 foetus and newborn infant. If treatment with β-adrenoceptor blockers is necessary, β_1-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 foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus 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.

4.7 Effects on ability to drive and use machines

In a study of 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 the start of treatment and upon change of medication as well as in conjunction with alcohol.

4.9. Overdose

There is no experience yet regarding overdosage of bisoprolol in patients with stable chronic heart failure. The most common signs expected with overdosage of a ß-blocker 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 interindividual 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.

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 pharmacological actions and recommendations for other ß-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 glucagon (initial dose 1 – 10 mg i.v., then 2 – 2.5 mg per hour as continuous infusion) 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, $ß_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

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Hypoglycaemia: Administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C07AB07

Bisoprolol is a highly $ß_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulation and relevant membrane stabilizing activity. It only shows low affinity to the $ß_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $ß_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $ß_2$-mediated metabolic effects. Its $ß_1$-selectivity extends beyond the therapeutic dose range.

Bisoprolol is already 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.

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 admissions 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.

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 hours effect after dosing once daily.

Bisoprolol is excreted from the body by two routes. 50% is metabolized 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 β-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

Tablet core:
Maize starch
Microcrystalline cellulose
Crospovidone
Anhydrous calcium hydrogen phosphate
Magnesium stearate
Colloidal anhydrous silica.

Film-coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Dimeticone 350
Iron oxide yellow (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
The shelf life for this product is 3 years.

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

6.5 Nature and contents of container
Blister packs of aluminium foil and PVC/PVDC in cartons.

Pack size: 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Zanza Healthcare Limited
Unit A1
Kingfisher Business Park
Hawthorne Road
Liverpool
L20 6PF

8 MARKETING AUTHORISATION NUMBER(S)

PL 15582/0023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/08/2006

10 DATE OF REVISION OF THE TEXT

24/08/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Bisoprolol 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg bisoprolol fumarate (2:1)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Ivory coloured, scored, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

3. Management of hypertension

4. Management of angina pectoris

4.2 Posology and method of administration

Adults: The usual dose is 10 mg once daily with a maximum recommended dose of 20 mg per day. In some patients 5 mg per day may be adequate. In patients with final stage impairment of renal function (creatinine clearance < 20 ml/min) or liver function, the dose should not exceed 10 mg bisoprolol once daily.

Elderly: No dosage adjustment is normally required, but 5 mg per day may be adequate in some patients; as for other adults, dosage may have to be reduced in cases of severe renal or hepatic dysfunction.

Children and adolescents under 18: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

Route of administration: Oral

4.3 Contraindications

Bisoprolol is contra-indicated in 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
- bradycardia (heart rate less than 60 beats/min prior to start of therapy)
- hypotension (systolic blood pressure < 100mmHg)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- untreated phaeochromocytoma (see Special Warnings and Precautions)
- metabolic acidosis
- hypersensitivity to bisoprolol or to any of the excipients

4.4 Special warnings and precautions for use

Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways diseases)
- concomitant treatment with inhalation anaesthetics (see Interactions section)
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked
- strict fasting
- ongoing desensitisation therapy
- AV block of first degree
- Prinzmetal's angina
- peripheral arterial occlusive disease (intensification of complaints may occur particularly during the start of therapy)

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

- NYHA class II heart failure
- insulin dependent diabetes mellitus (type I)
- impaired renal function (serum creatinine ≥ 300 μmol/l)
- impaired liver function
- patients older than 80 years
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

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 $ß_2$-stimulants may have to be increased.

As with other ß-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 ß-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 thyrotoxicosis may be masked.

In patients with ischaemic heart disease, treatment should not be withdrawn abruptly.

Combination with calcium antagonists, clonidine or monoamine oxidase inhibitors (except MAO-B inhibitors) is not recommended. See 'Interactions' section.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

Calcium antagonists such as verapamil and to a lesser extent diltiazem: Negative influence on contractility, atrio-ventricular conduction and blood pressure. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrioventricular block.

Clonidine: Increased risk of "rebound hypertension" as well as exaggerated decrease in heart rate and cardiac conduction.

Monoamineoxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of ß-blockers but also risk of hypertensive crisis.

Combinations to be used with caution

Calcium antagonists such as dihydropyridine derivatives (eg, nifedipine): increased risk of hypotension. In patients with latent cardiac insufficiency, concomitant treatment with beta-blocking agents may lead to cardiac failure.

Class-I antiarrhythmic drugs (e.g. disopyramide, quinidine): Effect on atrial conduction time may be potentiated and negative inotropic effect may be increased.

Class-III antiarrhythmic drugs (e.g. amiodarone): Effect on atrial conduction time may be potentiated.

Parasympathomimetic drugs (including tacrine): Atrio-ventricular conduction time may be increased.

Other ß-blockers, including eye drops, have additive effects.

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

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension. Continuation of ß-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving bisoprolol.

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

Prostaglandin synthetase inhibiting drugs: Decreased hypotensive effects.

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

Sympathomimetic agents: Combination with bisoprolol may reduce the effect of both agents. Higher doses of epinephrine may be necessary for treatment of allergic reactions.

Tricyclic antidepressants, barbiturates, phenothiazines as well as other antihypertensive agents: Increased blood pressure lowering effect.

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.

Moxisylyte: Possibly causes severe postural hypertension.

Combinations to be considered

Mefloquine: increased risk of bradycardia

4.6 Pregnancy and lactation

Pregnancy

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, β-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 foetus and newborn infant. If treatment with β-adrenoceptor blockers is necessary, β_1-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 foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus 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.

4.7 Effects on ability to drive and use machines

In a study of 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 the start of treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

Clinical trial data

The table below shows incidences of adverse events reported from both the placebo and the bisoprolol cohort of the CIBIS II trial. Regardless of causal relationship all adverse events are included. Each patient is only counted once for each adverse event occurring in at least 5% of the study population.

Preferred Term WHO	Placebo (n=1321)		Bisoprolol (n=1328)	
	Pat. with AE	% Pat. with AE	Pat. with AE	% Pat. with AE
Cardiac failure	301	22.8	244	18.4
Dysponea	224	17.0	183	13.8
Dizziness	126	9.5	177	13.3
Cardiomyopathy	132	10.0	141	10.6
Bradycardia	60	4.5	202	15.2
Hypotension	96	7.3	152	11.4
Tachycardia	144	10.9	79	5.9
Fatigue	94	7.1	123	9.3
Viral infection	75	5.7	86	6.5

Pneumonia	69	5.2	65	4.9

AE = Adverse Events

Post-marketing data

The following data result from post-marketing experience with bisoprolol in the indications hypertension and coronary heart disease. There are no post-marketing data available for bisoprolol in the indication stable chronic heart failure.

Common (≥ 1% and <10%)	*Circ:* Feeling of coldness or numbness in the extremities *CNS:* Tiredness*, exhaustion*, dizziness*, headache* *GI:* Nausea, vomiting, diarrhoea, constipation
Uncommon (≥ 0.1% and <1%)	*General:* Muscular weakness and cramps *Circ:* Bradycardia, disturbance of AV conduction, worsening of heart failure, orthostatic hypotension *CNS* : Sleep disturbances, depression *Airways* : Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.
Rare (≥ 0.01% and <0.1%)	*CNS* : Nightmares, hallucinations *Skin* : hypersensitivity reactions (itching, flush, rash) *Liver* : increased liver enzymes (ALAT, ASAT), hepatitis *Metabolism* : Increased triglycerides *Urogenital* : Potency disorders *Ear-nose-throat* : hearing impairment, allergic rhinitis

	Eyes : reduced tear flow (to be considered if the patient uses lenses)
Very rare (< 0.01%)	*Eyes:* conjunctivitis, visual disturbances *Skin* : β-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia *Circ* : chest pain

* These symptoms especially occur at the beginning of the therapy. They are generally mild and often disappear within 1-2 weeks.

4.9 Overdose

There is no experience yet regarding overdosage of bisoprolol in patients with stable chronic heart failure. The most common signs expected with overdosage of a ß-blocker 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 interindividual 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.

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 pharmacological actions and recommendations for other ß-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 glucagon (initial dose 1 – 10 mg i.v., then 2 – 2.5 mg per hour as continuous infusion) 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, $ß_2$-

sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C07AB07

Bisoprolol is a highly $ß_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulation and relevant membrane stabilizing activity. It only shows low affinity to the $ß_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $ß_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $ß_2$-mediated metabolic effects. Its $ß_1$-selectivity extends beyond the therapeutic dose range.

Bisoprolol is already 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.

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 admissions 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.

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 hours effect after dosing once daily.

Bisoprolol is excreted from the body by two routes. 50% is metabolized 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 β-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

Tablet core:
Maize starch
Microcrystalline cellulose
Crospovidone
Anhydrous calcium hydrogen phosphate
Magnesium stearate
Colloidal anhydrous silica.

Film-coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 6000
Dimeticone 350
Iron oxide yellow (E172).

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The shelf life for this product is 3 years.

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

6.5 Nature and contents of container
Blister packs of aluminium foil and PVC/PVDC in cartons.

Pack size: 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Zanza Healthcare Limited
Unit A1
Kingfisher Business Park
Hawthorne Road
Liverpool
L20 6PF

8 MARKETING AUTHORISATION NUMBER(S)

PL 15582/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/08/2006

10 DATE OF REVISION OF THE TEXT

24/08/2006

PATIENT INFORMATION LEAFLET

BISOPROLOL 5mg 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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Bisoprolol 5mg Tablets

- Each tablet contains 5mg of the active ingredient bisoprolol fumarate.
- The other ingredients are maize starch, microcrystalline cellulose, crospovidone, anhydrous calcium hydrogen phosphate, magnesium stearate, colloidal anhydrous silica, hypromellose, titanium dioxide (E171), macrogol, dimeticone and iron oxide yellow (E172).

Each pack contains 28 tablets.

Bisoprolol belongs to a group of medicines called beta-blockers.

Marketing Authorisation Holder: Zanza Healthcare Limited, Unit A1, Kingfisher Business Park, Hawthorne Road, Liverpool, L20 6PF.

Manufacturer: Rottendorf Pharma GmbH, Ostenfelder Strasse 51-61, 59320 Ennigerloh, Germany.

1. WHAT BISOPROLOL 5mg TABLETS ARE AND WHAT ARE THEY USED FOR

Bisoprolol 5mg Tablets are used to treat high blood pressure and angina pectoris.

2. BEFORE YOU TAKE BISOPROLOL 5mg TABLETS

Do not take Bisoprolol 5mg Tablets before checking with your doctor again if:
- you are allergic to bisoprolol or any of the other ingredients of Bisoprolol 5mg Tablets
- you are in acute heart failure or if you require injection of inotropic drugs (drugs which increase the force of contraction of the heart)
- you have had cardiogenic shock (a condition in which your heart is unable to pump enough blood to your body)
- you suffer from heart block and do not have a pacemaker
- your suffer from low heart rate or your heart rate is abnormal because of a condition known as sick sinus syndrome
- you have very poor circulation or Raynaud's Syndrome
- you have unusually low blood pressure
- you have a tumour of the adrenal gland (phaeochromocytoma)
- you suffer from severe asthma or have severe breathing difficulties
- you suffer from metabolic acidosis (a disorder of the metabolism which causes the blood to become acidic)

Tell your doctor if you suffer from any of the following:
- heart failure (the treatment of heart failure is very different)
- asthma and any other lung disease
- diabetes mellitus (sugar diabetes)
- a history of allergies, including any for which you are undergoing desensitising treatment
- first degree heart block
- chest pain at rest
- poor circulation
- psioriasis (a type of rash)
- an overactive thyroid
- a tumour of the adrenal gland (phaeochromocytoma) which is being treated with drugs
- if you are taking treatment for depression, high blood pressure or migraine (e.g. Clonidine)
- kidney disease
- liver disease

If you go into hospital to have an operation, tell the anaesthetist and other medical staff that you are taking Bisoprolol 5mg Tablets.

You should also tell your doctor if:
- you are pregnant, planning to become pregnant or breast-feeding
- you are fasting

Take special care with Bisoprolol 5mg Tablets if:
- you suffer from allergies, because your allergic reaction may be more severe than otherwise
- you are taking other medicines – even those not prescribed to you by a doctor. Examples are drugs to treat heart disease, high blood pressure, irregular heart beat, angina, poor circulation, epilepsy, depression, mental illness, migraine, pain or diabetes. Also anaesthetics, eye/nose drops, cough medicines, anti-malarials or Rifampicin (an antibiotic).

Driving and operating machinery
- You may find that your reactions are impaired, especially if you have also drunk alcohol, particularly during the first few weeks of your treatment.

3. HOW TO TAKE BISOPROLOL 5mg TABLETS

Always take Bisoprolol 5mg Tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual dose for adults is: two tablets (10mg) daily. Your doctor may decide to increase or decrease this dose. The dose should not exceed 20mg in one day.

Children: Not recommended.

Elderly: the usual dose is the adult dose. A lower dose may be adequate.

Swallow the tablets whole with a drink of water or milk.

If you have the impression that the effect of Bisoprolol 5mg Tablets is too strong or too weak, talk to your doctor or pharmacist.

How long should you carry on taking Bisoprolol 5mg Tablets?
Make sure you do not run out of your tablets.
Do not stop taking your tablets without talking to your doctor first. In some cases, it may be necessary to stop taking your medicine gradually.

If you take more Bisoprolol 5mg Tablets than you should:
If you take too many tablets, tell your doctor or hospital casualty department straight away. Take your tablets with you.

If you forget to take Bisoprolol 5mg Tablets:
If you forget to take a dose, take it as soon as you remember, then go on as before. Never double up on the next dose to make up for the missed.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Bisoprolol 5mg Tablets can have side effects.

Common side effects (between 1 in 10 and 1 in 100 patients) are a feeling of coldness or numbness in the fingers or toes, tiredness, exhaustion, dizziness, headache, nausea, vomiting, diarrhoea or constipation.

Uncommon side effects (between 1 in 100 and 1in 1,000 patients) include muscle weakness and cramps, interference with the normal heart rate, worsening of heart failure, low blood pressure upon standing up, sleep disturbances, depression or worsening of breathing problems.

Rare side effects (between 1 in 1,000 and 1 in 10,000 patients) are nightmares, hallucinations, skin reactions (itching, flushing, rash); hepatitis and increased liver enzymes (you would notice a yellowing of your skin or the whites of your eyes), increased blood levels of some fats, impotence, hearing loss, runny nose or dry eyes.

Very rare side effects (less than 1 in 10,000 patients) are conjunctivitis, visual disturbances, worsening of psoriasis or the development of a psoriasis-like rash, alopecia (hair loss) or chest pain.

Patients with heart failure may suffer from shortness of breath, a lowered heart rate, dizziness, low blood pressure, an increased heart rate, fatigue, viral infection or pneumonia.

Do not be alarmed, most people take Bisoprolol 5mg Tablets without any problems.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING BISOPROLOL 5mg TABLETS
Keep out of the reach and sight of children.

Do not store above 30°C.

Do not use after the expiry date stated on the blister strip and carton.

This leaflet was prepared in July 2006 PL15582/023

BISOPROLOL 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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

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1. WHAT BISOPROLOL 10mg TABLETS ARE AND WHAT ARE THEY USED FOR

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- your suffer from low heart rate or your heart rate is abnormal because of a condition known as sick sinus syndrome
- you have very poor circulation or severe Raynaud's Syndrome
- you have unusually low blood pressure
- you have a tumour of the adrenal gland (phaeochromocytoma) which is not currently being treated
- you suffer from severe asthma or have severe breathing difficulties
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Tell your doctor if you suffer from any of the following:
- heart failure (the dosage regimen for the treatment of stable chronic heart failure with bisoprolol is very different to that for the treatment of angina and high blood pressure)
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- diabetes mellitus (sugar diabetes)
- a history of allergies, including any for which you are undergoing desensitising treatment
- first degree heart block
- chest pain at rest
- poor circulation
- psioriasis (a type of rash)
- an overactive thyroid
- a tumour of the adrenal gland (phaeochromocytoma) which is being treated with drugs
- a condition being treated with a monoamine oxidase inhibitor (e.g. depression) or a calcium antagonist (e.g. angina or high blood pressure) or clonidine (e.g. migraine or high blood pressure)
- kidney disease
- liver disease

If you go into hospital to have an operation, tell the anaesthetist or other medical staff that you are taking Bisoprolol 10mg Tablets.

You should also tell your doctor if:
- you are pregnant, planning to become pregnant or breast-feeding
- you are fasting
- you are taking other medicine – even those not prescribed to you by a doctor. Examples are drugs to treat heart disease, high blood pressure, irregular heart beat, angina, poor circulation, epilepsy, depression, mental illness, migraine, pain or diabetes. Also anaesthetics, eye/nose drops, cough medicines, anti-malarials or Rifampicin (an antibiotic).

Take special care with Bisoprolol 10mg Tablets if:
- you suffer from allergies, because your allergic reaction may be more severe than otherwise
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Very rare side effects are conjunctivitis, visual disturbances, worsening of psoriasis or the development of a psoriasis-like rash, alopecia (hair loss) or chest pain.

Do not be alarmed, most peoples take Bisoprolol 10mg Tablets without any problems.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING BISOPROLOL 10mg TABLETS

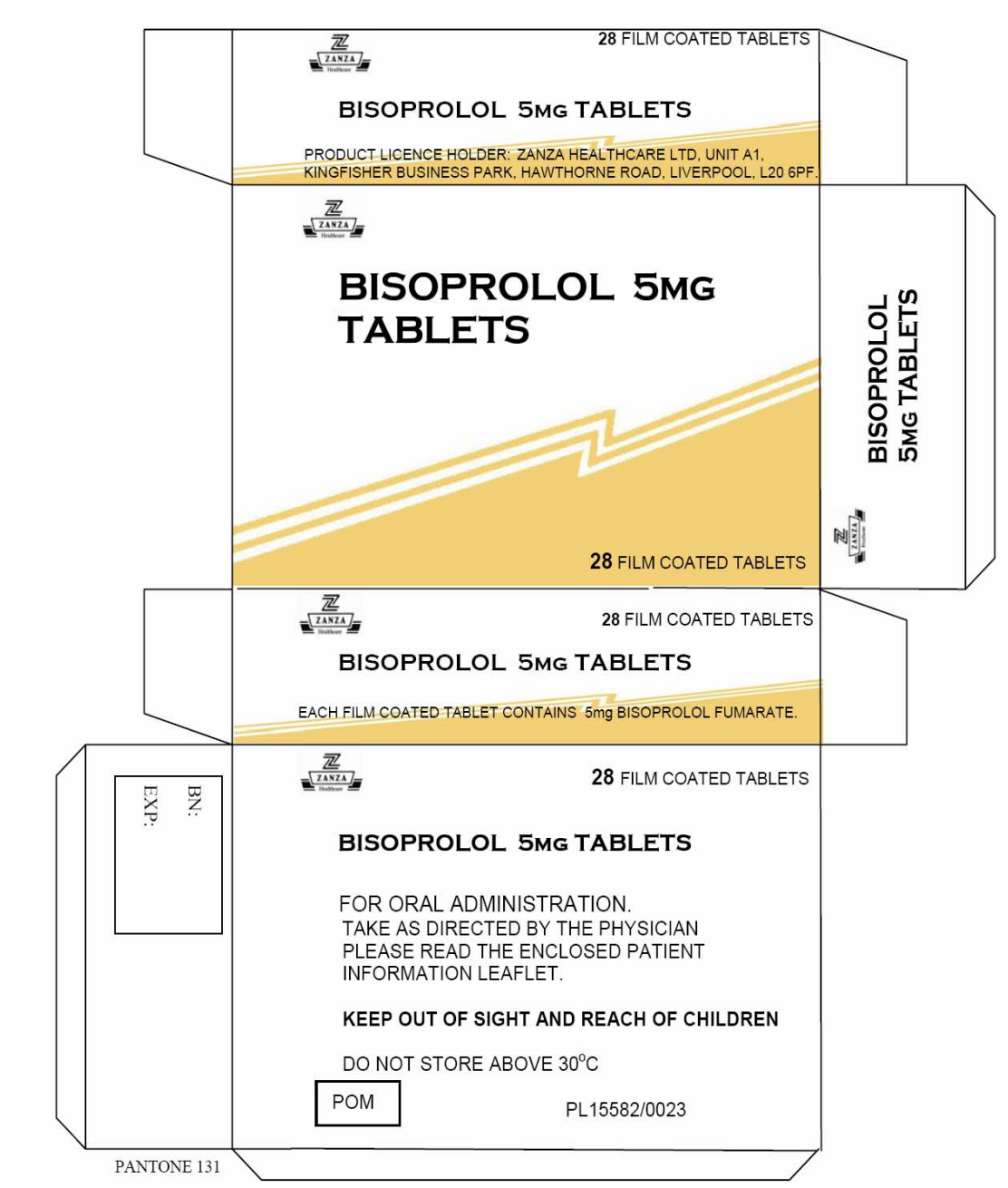
Keep out of the reach and sight of children.

Do not store above 30°C.

Do not use after the expiry date stated on the blister strip and carton.

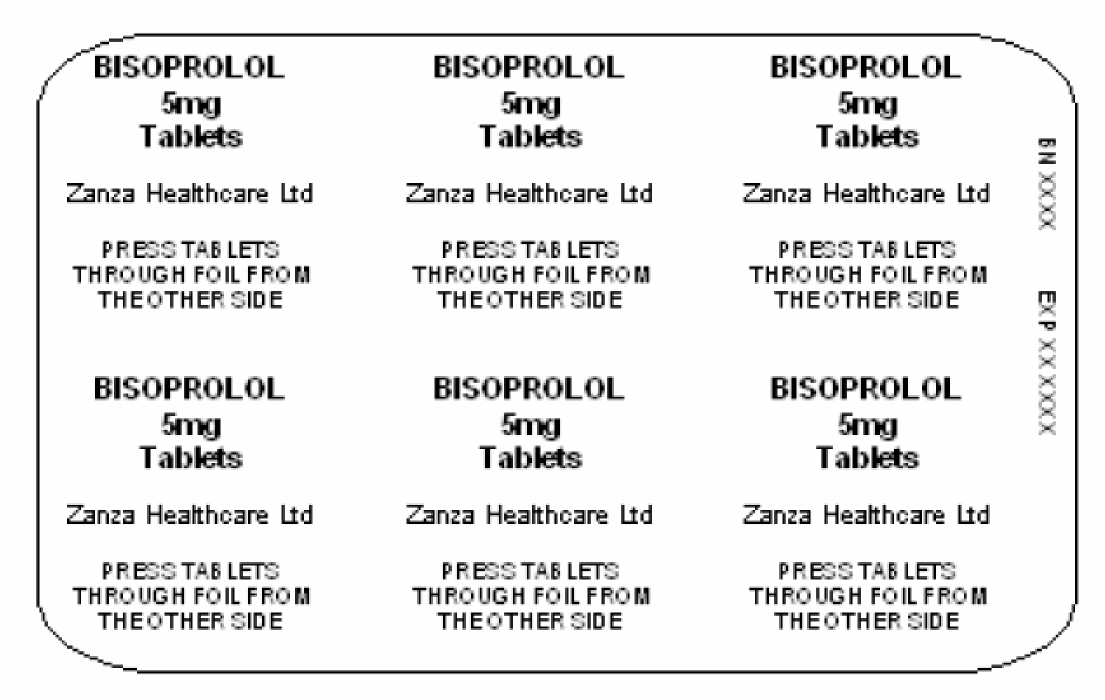
This leaflet was prepared in October 2004 PL15582/024

PACKAGING



BRAILLE TO GO ON PACK FRONT:

BISOPROLOL
$5mg TABLETS


BISOPROLOL
5mg
Tablets
Zanza Healthcare Ltd
PRESS TABLETS
THROUGH FOIL FROM
THE OTHER SIDE
BISOPROLOL
5mg
Tablets
Zanza Healthcare Ltd
PRESS TABLETS
THROUGH FOIL FROM
THE OTHER SIDE
BISOPROLOL
5mg
Tablets
Zanza Healthcare Ltd
PRESS TABLETS
THROUGH FOIL FROM
THE OTHER SIDE
BN XXXX
EXP XX XXXX
BISOPROLOL
5mg
Tablets
Zanza Healthcare Ltd
PRESS TABLETS
THROUGH FOIL FROM
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PRESS TABLETS
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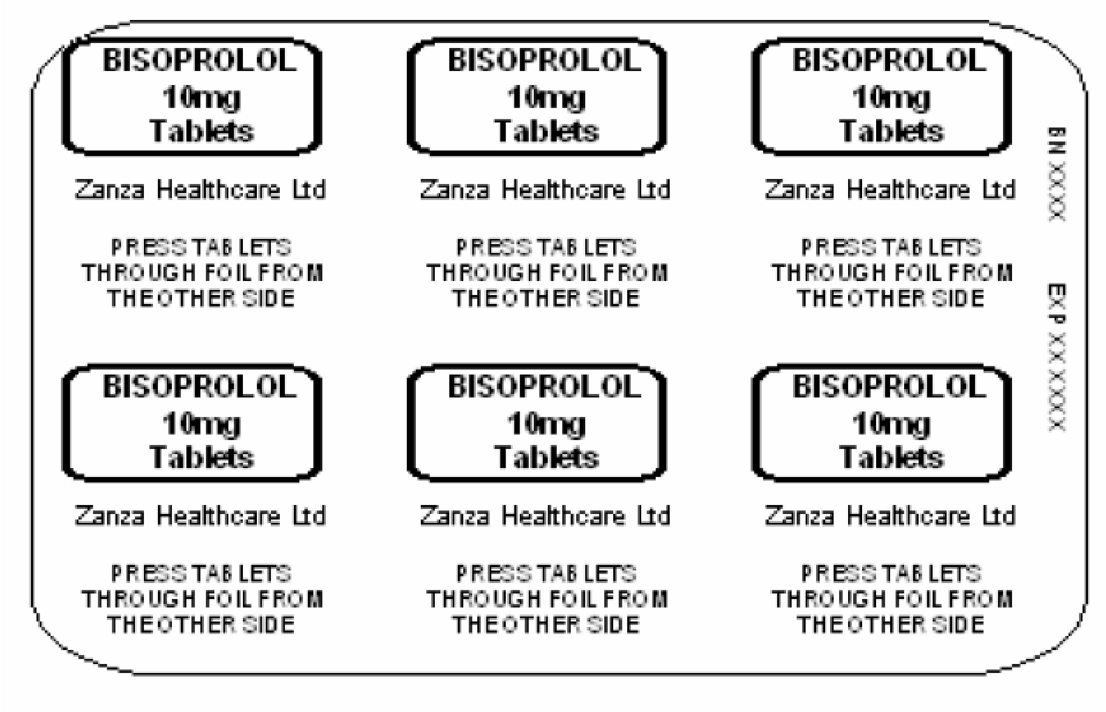
THE OTHER SIDE
BISOPROLOL
5mg
Tablets
Zanza Healthcare Ltd
PRESS TABLETS
THROUGH FOIL FROM
THE OTHER SIDE

BRAILLE TO GO ON PACK FRONT:

BISOPROLOL
$10mg TABLETS


BISOPROLOL
10mg
Tablets
Zanza Healthcare Ltd
PRESS TABLETS THROUGH FOIL FROM THE OTHER SIDE
BN XXXX
EXP XX XXXX