SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bisoprolol fumarate 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film-coated Tablet contains 5 mg of bisoprolol fumarate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
The 5 mg film-coated tablets are white, round and convex with the following identification markings: BISOPROLOL 5 engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension.
Treatment of chronic stable angina pectoris.

4.2 Posology and method of administration

Posology

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.

Renal impairment
In patients with severe renal impairment, (creatinine clearance < 20ml/min) the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

Severe hepatic impairment
In patients with severe liver function disorders it is recommended that a daily dose of 10 mg bisoprolol fumarate is not exceeded.

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

Paediatric population

Children under 12 years and adolescents under 18 years
There is no paediatric experience with this medicine, therefore its use cannot be recommended for children.

Method of administration
Bisoprolol fumarate 5 mg tablets are for oral administration.

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

4.3 Contra-indications

- hypersenitivity to the active substance or to any of the excipients listed in section 6.1.
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree (without a pacemaker)
- sick sinus syndrome
- sinoatrial block
- symptomatic bradycardia with less than 60 beats/min before start of therapy
- symptomatic hypotension (systolic blood pressure less than 100 mm Hg)
- severe bronchial asthma or severe chronic obstructive pulmonary disease
- late stages of peripheral arterial occlusive disease and Raynaud's syndrome
- metabolic acidosis
- untreated phaeochromocytoma (see section 4.4).
- combinations with floctafenine and sultopride (see also section 4.5).

4.4 Special warnings and precautions for use

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

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

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

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

Bisoprolol must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways disease): In bronchial asthma or other chronic obstructive airway diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of β2-stimulants may have to be increased. It is recommended to have a functional respiratory test done before the initiation of treatment.

- concomitant treatment with anticholinesterastic drugs (including tacrine): 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 section 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. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

- iodated contrast products: Beta-blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodated contrast products

- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked. Blood glucose levels should be monitored during treatment with bisoprolol

- thyreotoxicosis, adrenergic symptoms may be masked

- strict fasting

- ongoing desensitisation therapy: As with other β-blocking agents bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline treatment does not always give the expected therapeutic effect. Higher doses of epinephrine (adrenaline) may be necessary

- AV block of first degree

- Prinzmetal's angina: β-blocking agents may increase the number and duration of anginal attacks in patients with Prinzmetal's angina. The use of β-1 selective adrenoceptor blocking agents is possible in cases of mild forms and only in combination with a vasodilating agent.

- Peripheral circulatory disorders, such as Raynaud's phenomena and 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

- 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. (see section 4.2)

Excipient(s)

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended
Calcium antagonists (verapamil, diltiazem, bepridil): negative influence on contractility, atrio-ventricular conduction and blood pressure (see also section 4.4). Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Clonidine and other centrally-acting antihypertensive drugs, i.e. methyldopa, guanfacin, moxonidine, rilmenidine: Concomitant use of centrally-acting antihypertensive drugs may lead to reduction of heart rate and cardiac output and to vasodilatation. Abrupt withdrawal may increase the risk of 'rebound hypertension'.

Fingolimod

Potentiation of bradycardic effects which may have fatal consequences. Patients using beta-blockers are in particular at risk as they prevent the mechanisms of adrenergic compensation. Clinical monitoring and continuous ECG for 24 hours after the first dose of fingolimod is required.

Combinations to be used with caution
Class I antiarrhythmic active substances (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)

Class III antiarrhythmic active substances (e.g. amiodarone): effect on atrial conduction time may be potentiated (see section 4.4).

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

Calcium antagonists (dihydropyridine derivatives): increased risk of hypotension. In patients with latent heart failure concomitant use of β-blocking agents can lead to heart failure

Anticholinesterastic drugs (including tacrine): atrio-venticular conduction time and/or bradycardia may be increased (see also section 4.4).

Other β-blocking agents, including topical (eye-drops for glaucoma treatment), may add to the systemic effects of bisoprolol.

Insulin and oral anti-diabetic active substances: 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.

Beta-sympathomimetic agents (e.g. isoprenaline, dobutamine): combination with bisoprolol may reduce effects of both agents.

Sympathomimetics that activate both beta- and alpha-adrenoceptors (e.g. norepinephrine, epinephrine): combination with bisoprolol may unmask the alpha-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 beta-blockers.

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

Baclofen: increased antihypertensive activity

Amifostine: increased hypotensive activity

NSAIDs: decrease of the antihypertensive effect of bisoprolol (inhibition of vasodilatative prostaglandin by NSAID and water and sodium retention with pyrazolone NSAID)

Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential may increase the risk of hypotension.

Combinations to be considered
Mefloquine: increased risk of bradycardia.

Corticosteroids: decrease of antihypertensive effect due to water and sodium retention.

Monoamine oxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the betablockers but also risk of hypertensive crisis.

Rifampicin: Slight reduction of the half-life of bisoprolol possible due to the induction of hepatic drugmetabolising enzymes. Normally no dosage adjustment is necessary

4.6 Fertility, pregnancy and lactation

Pregnancy
Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, 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 foetus and newborn infant. If treatment with β-adrenoceptor blocking agents is necessary, β_1-adrenoceptor blocking agents are preferable.

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

Breast-feeding
It is not known whether 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 patients bisoprolol did not impair driving performance. However, due to individual variations in reactions to the medicinal product, the ability to drive a vehicle or to operate machinery may be impaired. This should be considered particularly at start of the treatment and upon change of medication as well as in conjunction with alcohol.

4.8 Undesirable effects

The reported 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 (≥1/10),
Common (≥1/100to <1/10),
Uncommon (≥1/1,000to <1/100),
Rare (≥1/10,000to <1/1,000),
Very rare (<1/10to000)
Not known (cannot be estimated from the available data)

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

Metabolism and nutrition disorders
Rare: hypoglycaemia

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

Nervous system disorders

Common: dizziness, headache (especially at the beginning of the therapy, they are generally mild and often disappear within 1-2 weeks)
Rare: Syncope

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

Ear and labyrinth disorders
Rare: Hearing impairment

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

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

Respiratory, thoracic and mediastinal disorders

Uncommon: Bronchospasm in patients with bronchial asthma or a history of obstructive airway disease
Rare: allergic rhinitis

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

Hepatobiliary disorders
Rare: hepatitis

Skin and subcutaneous tissue disorders:
Rare: Hypersensitivity reactions (itching, flush, rash and angioedema)
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: Erectile dysfunction

General Disorders and administration site conditions
Common: fatigue (especially at the beginning of the therapy. generally mild and offen disappear within 1-2 weeks.)
Uncommon: asthenia

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

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
The most common signs expected with overdosage of bisoprolol are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is a wide inter-individual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

Management
In the case of overdosage, bisoprolol treatment should be stopped and supportive and symptomatic treatment should be provided. Resorption of bisoprolol in the gastrointestinal tract must be avoided; gastric lavage, or administration of adsorbents (i.e. activated charcoal), and a laxative agent (i.e. sodium sulphate) may be used. Respiration must be monitored and if necessary, artificial respiration should be initiated. Bronchospasm should be counteracted with bronchodilator therapy such as isoprenaline or β_2-sympathicomimetic active substances. Cardiovascular complications should be treated symptomatically: AV-block (second or third degree) needs careful monitoring and be treated with isoprenaline infusion or transvenous cardiac pacemaker insertion. Bradycardia should be treated with intravenous atropine (or M-methyl-atropine). Fall in blood pressure or shock should be treated

with plasma substituting agents and vasopressors. Hypoglycaemia can be treated with i.v.-glucose. Limited data suggest that bisoprolol is hardly dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents,selective, ATC code: C07AB07

Mechanism of action
Bisoprolol is a potent, highly β,-selective-adrenoceptor blocking agent devoid of intrinsic sympathomimetic activity and without relevant membrane stabilising activity. As with other β,-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. Hence bisoprolol is effective in eliminating or reducing the symptoms.

Bisoprolol possesses similar local anaesthetic properties to propranolol.

5.2 Pharmacokinetic properties

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

Biotransformation and Elimination:
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.

Linearity/non-linearity
The kinetics of bisoprolol are linear and independent of age.
In patients with chronic heart failure (NYHA stage III) the plasma levels of bisoprolol are higher and the half life is prolonged compared to healthy volunteers. Maximum plasma concentration at steady state is 64 ± 21 ng/ml at a daily dose of 10 mg and the half life is
17 ± 5 hours.

5.3 Preclinical safety data

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

toxicity (increased incidence of resorptions, reduced birth weight of the offspring, retarded physical development) at high doses was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose (E460)
Mannitol (E421)
Croscarmellose sodium
Magnesium stearate (E572)

Coating:
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 6000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Bottles: Keep the bottle tightly closed in order to protect from light and/or moisture .
Blisters: Keep the blister in the outer carton in order to protect from light and/or moisture.

6.5 Nature and contents of container

White, round polyethylene bottles with polyethylene caps with tamper evident ring.

Thermoformed transparent PVC/PVdC – aluminium blisters (PVC foil 250 µm thick, PVdC coating 23 µm, aluminium foil 20 µm thick).

Thermoformed white opaque PVC/PVdC- aluminium blisters (PVC foil 250 µm thick, PVdC coating 40 g/m², aluminium foil 20 µm thick).

20, 28, 30, 50, 56, 60, 84, 90, 98, 100 and 105 tablets in bottles or blisters packaging.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0376

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THEAUTHORISATION

24 January 2001

10. DATE OF REVISION OF THE TEXT

23/02/2023