Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet Bisoprolol fumarate 10 mg contains 8.49 mg bisoprolol equivalent to 10 mg bisoprolol fumarate.

Excipient with known effect
Each tablet contains 130.20 mg of lactose monohydrate per tablet

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Bisoprolol fumarate 10 mg tablets are mottled beige, round and convex with the following identification markings: BI centrally above a break-line with 10 below.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension
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.

Special Populations

Renal or liver impairment
Adjustment of dose in patients with mild to moderate liver- or kidney impairment is usually not necessary. In patients with severe renal impairment (creatinine clearance < 20 ml/min) or severe liver impairment, the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.

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

Paediatric population
Bisoprolol fumarate tablets are not recommended for use in children due to a lack of data (see section 5.3).

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.

Method of administration

Bisoprolol fumarate tablets are for oral administration.
The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet can be taken with or without food.

4.3 Contraindications

Bisoprolol is contraindicated in patients with

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- acute heart failure or during episodes of heart failure decompensation requiring i.v. inotropic therapy
- cardiogenic shock
- AV block of second or third degree
- 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
- severe forms of peripheral arterial occlusive disease or severe forms of 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 beta-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 fumarate must be used with caution in:

- bronchospasm (bronchial asthma, obstructive airways disease): In bronchial asthma or other chronic obstructive pulmonary diseases, which may cause symptoms, bronchodilating therapy should be given concomitantly. Occasionally an increase of the airway resistance may occur in patients with asthma, therefore the dose of $beta_2$-stimulants may have to be increased. It is recommended to have a functional respiratory test done before the initiation of treatment
- concomitant treatment with 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 beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving bisoprolol fumarate. If it is thought necessary to withdraw beta-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia
- iodated contrast products: Beta-blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock induced by iodated contrast products.
- diabetes mellitus with large fluctuations in blood glucose values; symptoms of hypoglycaemia can be masked. Blood glucose levels should be monitored during treatment with bisoprolol
- thyrotoxicosis, adrenergic symptoms may be masked
- strict fasting

- ongoing desensitisation therapy. As with other beta-blocking agents bisoprolol fumarate 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: beta-blocking agents may increase the number and duration of anginal attacks in patients with Printzmetal's angina. The use of $beta_1$ selective adrenoceptor blocking agents is possible in cases of mild forms and only in combination with a vasodilating agent.
- peripheral arterial occlusive diseases, 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 fumarate must not be administered until after alpha-receptor blockade
- pre-existing or existing psoriasis, Bisoprolol fumarate tablets should only be given after a thorough risk/ benefit assessment

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

Bisoprolol fumarate 5 mg, tablets contain 135.20 mg lactose monohydrate.
Bisoprolol fumarate 10 mg, tablets contain 130.20 mg lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Combinations contra-indicated
Floctafenine: beta-blockers may impede the compensatory cardiovascular reactions associated with hypotension or shock that may be induced by floctafenine.

Sultopride: bisoprolol fumarate should not be concomitantly administered with sultopride since there is an increased risk of ventricular arrhythmia.

Combinations not recommended
Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative effect on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on beta-blocker treatment may lead to profound hypotension and atrio-ventricular block.

Centrally-acting antihypertensive drugs (e.g. clonidine, 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'.

Monoamineoxidase inhibitors (except MAO-B inhibitors): Enhanced hypotensive effect of the beta-blocker but also risk for hypertensive crisis.

Combinations to be used with caution
Class I antiarrhythmic drugs (e.g. disopyramide, quinidine): effect on atrioventricular conduction time may be potentiated and negative inotropic effect may be increased. (Strict clinical and ECG monitoring is required).

Class III antiarrhythmic drugs (e.g. amiodarone): effect on atrio-ventricular conduction time may be potentiated (see section 4.4).

Calcium antagonists of the dihydropyridine type: 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.

Parasympathomimetic drugs (including tacrine); atrio-ventricular conduction time and/or bradycardia may be increased (see also section 4.4).

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

Insulin and oral anti-diabetic drugs: Increase of blood sugar lowering effect. Blockade of beta-adrenoceptor may mask symptoms of hypoglycaemia.

Digitalis glycosides: reduction in 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 fumarate 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 and other drugs with blood pressure lowering potential: increased risk of hypotension.

Baclofen: increased antihypertensive activity.

Amifostine: increased hypotensive activity.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol. (inhibition of vasodilative prostaglandin by NSAID and water and sodium retention with pyrazolone NSAID).

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 beta-blockers 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 fumarate has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-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 beta-adrenoceptor blocking agents is necessary, $beta_1$-adrenoceptor blocking agents are preferable.
Bisoprolol fumarate should not be used during pregnancy unless clearly necessary. If treatment with bisoprolol fumarate 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 should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.

Breastfeeding:

It is not known whether bisoprolol fumarate is excreted in human milk. Therefore breastfeeding is not recommended during administration of Bisoprolol fumarate tablets.

4.7 Effects on ability to drive and use machines

This medicinal product could have a minor influence on the ability to drive and use machines.
In a study with coronary heart disease patient's bisoprolol did not impair driving performance. However, due to individual variations in reactions to the medicinal product, the ability to drive a vehicle or to operate machinery may be impaired. 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 following terminologies have been used in order to classify the occurrence of undesirable effects:

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

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

Metabolism and nutrition disorders
Rare: Increased triglycerides, hypoglycaemia
Very rare: Hypoglycaemic shock

Psychiatric disorders
Uncommon: Sleepdisorders, depression
Rare: Nightmares, hallucinations

Nervous system disorders
Common: Tiredness, exhaustion, 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 disorders

Cardiac disorders
Uncommon: Bradycardia, AV- conduction 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, hypotension, Raynaud's disease, increase of existing intermittent claudication
Uncommon: Orthostatic hypotension

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

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

Hepatobiliary disorders
Rare: Hepatitis

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

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

Reproductive system and breast disorders
Rare:Potency disorders

General disorders and administration site conditions
Common: Fatigue*
Uncommon: Asthenia

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Symptoms
The most common signs expected with overdose of a beta-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. Bradycardia and/or hypotension were noted. All patients recovered. 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 general, if overdose occurs, bisoprolol treatment should be discontinued and supportive and symptomatic treatment should be provided. Based on the expected pharmacological actions and recommendations for other beta-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 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.

Bronchospasms: Administer bronchodilator therapy such as isoprenaline, $beta_2$-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia:
Administer i.v. glucose.

Limited data available suggest that bisoprolol is hardly dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Bisoprolol is a potent highly beta-1 selective-adrenoceptor blocking agent devoid of intrinsic sympathomimetic activity. As with other beta-1 blocking agents, the mode of action in hypertension is unclear. However, it is known that bisoprolol fumarate markedly depresses plasma renin activity.
In patients with angina, the blockade of beta-receptors reduces heart action and thus reduces oxygen demand.

Bisoprolol possesses similar local anaesthetic properties to propranolol.

5.2 Pharmacokinetic properties

Bisoprolol is absorbed almost completely from the gastrointestinal tract. Together with the very small first pass effect in the liver, this results in a high bioavailability of approximately 90%. The plasma protein binding of bisoprolol is about 30 %. The distribution volume is 3.5 l/kg. The total clearance is approximately 15 l/h.
The plasma elimination half-life (10-12 hours) provides 24 hours efficacy following a once daily dosage.
Bisoprolol is excreted from the body by two routes, 50 % is metabolised by the liver to inactive metabolites which are then excreted by the kidneys. The remaining 50 % is excreted by the kidneys in an unmetabolised form. Since elimination takes place in the kidneys and the liver to the same extent a dosage adjustment is usually not required for patients with mild to moderate impaired liver function or renal insufficiency. In patients with severe renal impairment (creatinine clearance < 20 ml/min) or severe liver impairment, the dose should not exceed 10 mg once daily. This dosage may eventually be divided into halves.
The kinetics of bisoprolol fumarate 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenicity. Like other beta-blocking agents, bisoprolol fumarate 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

Lactose monohydrate
Cellulose, microcrystalline
Magnesium stearate
Crospovidone
Beige PB 27215 (lactose monohydrate and iron oxides red and yellow (E172))

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Bisoprolol 10mg tablets are presented in:
Blisters comprising of PVC/PVdC/aluminium foil, contained within a printed carton box.
Pack sizes; 10, 20, 28, 30, 50, 56, 60 or 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/097/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010
Date of last renewal: 30th November 2011

10 DATE OF REVISION OF THE TEXT

December 2018