SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains bisoprolol as 10mg of bisoprolol fumarate.

Refer to Section 6.1 for excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Description: Round, biconvex, light brown coloured, film-coated tablets with a scoreline on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Management of hypertension.

Management of angina pectoris.

4.2 Posology and method of administration

Route of Administration

Oral

Posology

Adults: The usual dose is 10mg once daily with a maximum recommended dose of 20mg per day. In some patients 5mg per day may be adequate.

Experience of the use of bisoprolol fumarate in renal dialysis patients is limited; however, there is no evidence that the dosage regimen needs to be altered.

Elderly: No dosage adjustment is normally required but 5mg 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: There is no paediatric experience with bisoprolol, therefore its use cannot be recommended for children.

Renal impairment: In patients with final stage impairment of renal (creatinine clearance <20ml/min), use a maximum 10mg daily in severe renal impairment

Severe liver impairment: Maximum 10mg daily in severe liver impairment

4.3 Contraindications

As with other beta-adrenoceptor antagonists bisoprolol fumarate should not be used in cases of:

- Hypersensitivity to bisoprolol fumarate or any other ingredients in the tablet.
- Acute heart failure or during episodes of heart failure decompensation requiring iv inotropic therapy.
- Cardiogenic shock.
- Marked bradycardia (heart rate less than 60 beats per minute prior to start of therapy).
- Sinoatrial block
- Second or third degree AV block (without a pacemaker)
- Sick sinus syndrome.
- Extreme hypotension (systolic blood pressure < 100mmHg)
- Severe bronchial asthma or severe chronic obstructive pulmonary disease
- Later stages of peripheral arterial occlusive disease and Raynaud's syndrome
- Untreated phaeochromocytoma (see section 4.4)

Metabolic acidosis

4.4 Special warnings and precautions for use

Bisoprolol must be used with caution in:

- Heart failure (the treatment of stable chronic heart failure with bisoprolol has to be initiated with a special titration phase [for details, see SPC for bisoprolol indicated for the treatment of stable chronic heart failure])
- Bronchospasm (bronchial asthma, obstructive airways disease)

- Concomitant treatment with inhalation anaesthetics (see section 4.5)
- 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).

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 β2 stimulants may have to be increased.

As with other β-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 β-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 section 4.5.

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 atrio-ventricular block.

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

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

Combinations to be used with caution

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

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

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

Parasympathomimetic drugs: Atrio-ventricular conduction time may be increased.

Other β –blockers, including eye drops, have additive effects.

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

Anaesthetic agents: Attenuation of the reflex tachycardia and increase of the risk of hypotension. Continuation of β-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 effect.

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 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 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

Adverse reactions are ranked under headings of frequency, using the following convention:

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000), including isolated reports.

Very rare:

Eyes: conjunctivitis, visual disturbances

Skin: β-blockers may provoke or worsen psoriasis or induce psoriasis-like rash, alopecia

Cardiovascular: Chest pain

Rare:

CNS: Nightmares, Hallucinations

Skin: Hypersensitivity reactions (such as itching, flush, rash and angioedema)

Liver: Increased liver enzymes (ALAT, ASAT), hepatitis

Metabolism: Increased triglycerides

Urogenital: Potency disorders

Ear-Nose-Throat: hearing impairment, allergic rhinitis

Eyes: Reduced tear flow, dry eyes (to be considered if the patient uses lenses)

Uncommon:

Skeleto-muscular: Muscular weakness, pain and cramps

Circulatory: Bradycardia, disturbance of AV conduction, worsening of heart failure, orthostatic hypotension

CNS: Sleep disturbances (e.g. vivid dreams), depression

Airways: Bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.

Common:

Circulatory: Feeling of coldness or numbness in the extremities, oedema CNS: Tiredness*, exhaustion*, dizziness*, headache*

GI: Nausea, vomiting, diarrhoea, constipation Other effects: Perspiration

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

4.9 Overdose

The most common signs expected with overdosage of a β-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. To date a few cases of overdose (maximum: 2000mg) 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.

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 β-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.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, β_2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Bisoprolol fumarate is a potent, highly β1-selective-adrenoreceptor blocking agent devoid of intrinsic sympathomimetic activity and without relevant membrane stabilising activity.

As with other β1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol fumarate markedly depresses plasma renin activity.

In patients with angina, the blockade of β1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol fumarate is effective in eliminating or reducing the symptoms.

5.2 Pharmacokinetic properties

Bisoprolol fumarate 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 drug is cleared equally by the liver and kidney.

The plasma elimination half-life (10-12 hours) provides 24 hour efficacy following a once daily dosage. About 95% of the drug substance is excreted through the kidney, half of this is as unchanged bisoprolol. There are no active metabolites in man.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablet also contains:

Maize starch

Microcrystalline cellulose

Crospovidone

Calcium hydrogen phosphate

Magnesium stearate

Colloidal silica

The coating contains:

Hypromellose

Titanium dioxide (E171)

Macrogol

Dimeticone
Iron oxide (E172)

6.2 Incompatibilities

None known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30ºC. Store in the original packaging.

6.5 Nature and contents of container

Blister packs composed of PVC/PVdC that are covered by an aluminium lidding foil. The packs contain 28 tablets.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

MQ Consultancy Services Limited
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PL 60351/0002

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