

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Emcoretic Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg Bisoprolol fumarate and 12.5 mg Hydrochlorothiazide.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Circular, biconvex, pink, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Management of hypertension.

4.2 Posology and method of administration

Method of Administration: Oral.

Adults: One tablet daily.

In patients with moderate to severe impairment of renal (creatinine clearance < 20ml/min) or liver function the dose should be reduced.

Elderly: As for adults.

Children: There is no paediatric experience with bisoprolol and it is not therefore recommended for children.

4.3 Contraindications

It should not be used in cases of untreated or decompensated cardiac failure, cardiogenic shock, sinoatrial block, second or third degree AV block, marked bradycardia (heart rate less than 50 beats/min), acute myocardial infarction, severe asthma, patients with a known hypersensitivity to hydrochlorothiazide, severe renal or hepatic failure, hypokalaemia or hyponatraemia.

4.4 Special warnings and special precautions for use

Emcoretic can be administered with caution to patients with obstructive respiratory disorders provided that adequate supervision is maintained. If increased airways resistance develops consideration must be given to discontinuation of the β -blocker, depending on the degree of airways resistance and the benefit derived from β -blockade.

Use with care in patients with a prolonged PR conduction interval, poor cardiac reserve and peripheral circulatory

disturbances, such as Raynaud's phenomenon.

In patients with ischaemic heart disease, treatment should not be withdrawn abruptly.

Since bisoprolol is a highly selective β_1 -adrenoceptor antagonist, it may be used with caution in patients with a medical history of chronic obstructive airways disease. However, in some patients an increase in airways resistance may occur. This bronchospasm can usually be reversed by commonly used bronchodilators such as salbutamol.

Due to the low affinity of bisoprolol for β_2 -receptors, it does not appear to have a hypoglycaemic effect. However, it should be used with caution in diabetic patients since the symptoms of hypoglycaemia (in particular, tachycardia) may be masked and hydrochlorothiazide may impair glucose tolerance further.

Care should be taken in patients with a predisposition to gout or hyperuricaemia.

All patients treated with diuretics should receive periodic monitoring for signs of fluid or electrolyte imbalance. Hypokalaemia can be induced as a result of thiazide therapy and potassium levels should be checked, particularly in older patients, those receiving digitalis preparations for heart failure, those on diets low in potassium and patients suffering from gastro-intestinal complaints. The low dose of hydrochlorothiazide reduces the probability of a significant electrolyte imbalance occurring.

Prior to anaesthesia, the anaesthetist should be informed if the patient is taking this product. In cases of severe ischaemic heart disease, the risk/benefit of continuing treatment should be evaluated. Care should be taken when using volatile anaesthetics because of an increased hypotensive effect. Hydrochlorothiazide may increase the responsiveness to agents of the tubocurarine type.

4.5 Interaction with other medicinal products and other forms of interaction

Bisoprolol may potentiate the effect of other concurrently administered antihypertensive drugs. Concomitant treatment with reserpine, α -methyldopa and clonidine may cause an exaggerated decrease in heart rate and blood pressure. In particular, if clonidine is to be discontinued, this should not be done until treatment with bisoprolol/hydrochlorothiazide has been discontinued for several days.

It should also be used with care when myocardial depressants, inhibitors of AV conduction such as calcium antagonists of the verapamil and diltiazem type, or class I antidysrhythmic agents such as disopyramide are used concurrently.

The intravenous administration of calcium antagonists and antiarrhythmic agents is not recommended during therapy.

Lithium should not generally be administered with diuretics such as lithium clearance may be significantly reduced.

The concurrent use of rifampicin can reduce the elimination half life of bisoprolol, although an increase in dose is generally not necessary. The effects of insulin or oral hypoglycaemic agents may be potentiated when used concurrently with bisoprolol.

4.6 Pregnancy and lactation

No teratogenic effects have been demonstrated with bisoprolol in animal studies, but thiazide diuretics are not generally recommended for use during pregnancy. Beta-blockers administered in late pregnancy may cause bradycardia or hypotension in the foetus/neonate. Like other antihypertensive therapy, the benefits of use during pregnancy should be weighed against the possible hazard to mother and foetus. Whilst clinically relevant levels of bisoprolol may not appear in breast milk, hydrochlorothiazide does appear in the milk and if treatment is essential then the patients should stop breast feeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

It is usually well tolerated with reported side effects generally attributable to its pharmacological effects. These include lassitude, dizziness, mild headache, perspiration, aggravation of intermittent claudication or Raynaud's disease, paresthesia of the extremities. Occasionally, a marked decrease in blood pressure and pulse rate or a disturbance of AV conduction may be observed. Dry eyes and sleep disturbances noted with other β -blockers have not been reported for patients treated with this product but may, rarely, occur.

Diuretics can affect blood sugar.

4.9 Overdose

In the case of overdosage or a precipitous drop in pulse rate and/or blood pressure, treatment must be discontinued. If necessary, the following antidotes should be administered alone or consecutively: intravenous atropine 0.5-2.0 mg, intravenous orciprenaline 0.5 mg by slow intravenous injection; also glucagon may be given at a dose level of 1 to 5 mg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Bisoprolol is a potent, highly β_1 -antagonist devoid of intrinsic sympathomimetic activity and without relevant membrane stabilising activity.

As with other β_1 -antagonists, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin levels and reduces heart rate.

In patients with angina, the blockage of β_1 -receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.

Hydrochlorothiazide is a thiazide diuretic which has an antihypertensive action. The diuretic effect is the result of inhibition of active Na^+ transport from kidney tubules to blood, preventing the resorption of Na^+ . It also appears to decrease peripheral resistance resulting from relaxation of vascular smooth muscle, possibly caused by its phosphodiesterase inhibiting activity.

The combination of a β_1 -adrenoceptor antagonist and thiazide diuretic is well established in the treatment of hypertension and shows greater therapeutic efficacy than either active ingredient alone in mild to moderate essential hypertension.

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 drug is cleared equally by the liver and kidney.

The long plasma half-life (10-12 hours) provides 24 hours 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.

Hydrochlorothiazide is relatively well absorbed for the gastrointestinal tract with peak plasma levels obtained after about 2 hours. Elimination is biphasic with an elimination half-life of 9-13 hours. It is mainly excreted unchanged in the urine.

When administered together, there are no significant pharmacokinetic interactions between bisoprolol and hydrochlorothiazide.

5.3 Preclinical safety data

There are no additional data from animal studies which provide any further relevant information for use in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic calcium phosphate anhydrous
Microcrystalline cellulose
Colloidal anhydrous silica
Maize starch
Magnesium stearate
Hypromellose
Dimeticone
Titanium dioxide
Iron oxide red (E172)
Iron oxide black (E172)
Polyethylene glycol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottles with polyethylene screw cap containing 100 tablets.

Carton with ACLAR/PE/PVC/Aluminium foil blisters containing 28 tablets.

Carton with ACLAR/PE/PVC/Aluminium foil blisters containing 2 tablets (professional sample).

6.6 Instructions for use and handling

None.

7 MARKETING AUTHORISATION HOLDER

Merck Limited
Harrier House
High Street
West Drayton
Middlesex
UB7 7QG
UK

8 MARKETING AUTHORISATION NUMBER

PA 654/8/1

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