SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bisoprolol Fumarate 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg of the active ingredient bisoprolol fumarate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round tablets engraved with ‘Bisoprolol 5’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of hypertension.

Treatment of angina pectoris.

4.2 Posology and method of administration

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. In patients with final stage impairment of renal function (creatinine clearance <20ml/min) or liver function, the dose should not exceed 10mg bisoprolol once daily.

Experience of the use of bisoprolol 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.

Method of administration:

For oral administration.

4.3 Contraindications

Patients with:

- uncontrolled cardiac failure.
- cardiogenic shock.
- sinoatrial block.
- second or third degree AV block.
- marked bradycardia (heart rate less than 50 beats/min).
- extreme hypotension.
- Sick sinus syndrome
- Prinzmetal's (variant) angina.
- severe peripheral vascular disease (Raynaud's disease or syndrome, intermittent claudication).
- use of anaesthetics which depress the myocardial activity (e.g. cyclopropane and trichlorethylene).
- untreated phaeochromocytoma.

- a history of bronchospasm, bronchial asthma or chronic obstructive airways disease.
- metabolic acidosis (eg in some diabetics).
- after prolonged fasting.
- hypersensitivity to any of the ingredients in Bisoprolol Fumarate Tablets (either bisoprolol fumarate or any of the excipients listed in Section 6.1).

4.4 Special warnings and precautions for use

In patients with ischaemic heart disease, sudden withdrawal of beta-adrenoceptor blocking drugs may result in anginal attacks of increased frequency or severity. Therefore, withdrawal of bisoprolol in patients with ischaemic heart disease should be gradual. If necessary at the same time replacement therapy should be initiated to prevent exacerbation of angina.

Particular care is required with patients whose cardiac reserve is poor. Beta-adrenoceptor blocking drugs should be avoided in overt heart failure, although they may be used when cardiac failure has been controlled. A reduction in heart rate is a pharmacological effect of bisoprolol. In rare cases where symptoms may be attributable to the slow heart rate, the dose should be reduced. Due to negative effects on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Cardiac failure due to thyrotoxicosis may respond to bisoprolol alone, but if other adverse factors are also present it is important to control signs of failure with cardiac glycosides and diuretics. The symptoms of thyrotoxicosis may be masked in patients taking bisoprolol.

Bisoprolol modifies the tachycardia of hypoglycaemia and it may prolong the hypoglycaemic response to insulin. Care should be exercised during concomitant use of bisoprolol and hypoglycaemic therapy in patients with diabetes mellitus.

Hepatic function will deteriorate in patients with portal hypertension and hepatic encephalopathy may develop. It has been suggested that treatment with bisoprolol may increase the risk of developing hepatic encephalopathy.

Beta-blockers should be used with great caution in patients with peripheral circulatory disorders (Raynaud's disease/syndrome, intermittent claudication) as they may aggravate such disorders.

Care should be taken in prescribing beta-blockers to patients with a known risk of recurrence of psoriasis.

Care is required when transferring patients from clonidine to a beta-adrenoceptor blocking drug. If the two drugs are given concurrently, clonidine should not be discontinued until several days after the withdrawal of the beta-adrenoceptor blocking drug. Care is required when prescribing a beta-adrenoceptor blocking drug with Class I antidysrhythmic agents such as disopyramide. Beta-adrenoceptor blocking drugs should be used with caution in combination with verapamil where ventricular function is impaired. The combination should not be given to patients with conduction abnormalities, nor should either drug be administered intravenously within 48 hours of discontinuing the other. Care is required during parenteral administration of preparations containing adrenaline to patients receiving beta-adrenoceptor blocking drugs, as in rare instances vasoconstriction, hypertension and bradycardia may occur (see 4.5 Interactions).

Care is required when administering anaesthetic agents to patients receiving bisoprolol. The anaesthetist should always be informed of the use of a beta-adrenoceptor blocking drug. The risks and benefits of continued beta-blocking therapy in the peri-operative period should be carefully evaluated.

Bisoprolol should be used with caution in patients with renal impairment (see 4.2 Posology and Method of Administration).

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions, and may also reduce the response to adrenaline (epinephrine).

Bisoprolol should be used with caution in patients with myasthenia gravis, as beta-blockers have been associated with deterioration of symptoms in a few patients.

In patients with phaeochromocytoma, bisoprolol must not be administered until after alpha-receptor blockade.

4.5 Interaction with other medicinal products and other forms of interaction

Antimalarials	*eg mefloquine* Increased risk of bradycardia.
Calcium channel blockers:	*eg verapamil and diltiazem:* Potentiation of bradycardia, myocardial depression, hypotension, cardiac arrhythmias, risk of asystole (see 4.4 Special warnings and precautions for use).

	eg dihydropyridine derivatives such as nifedipine: Increased risk of hypotension. May lead to cardiac failure in patients with latent cardiac insufficiency.
Cardiac glycosides:	Bradycardia, asystole and heart block because of an additive depressant effect on cardiac conduction.
Class I antiarrhythmic drugs:	*eg disopyramide, quinidine and amiodarone:* Increased atrial conduction time and negative inotropic effect.
Sympathomimetic drugs:	Hypertension and bradycardia resulting from enhanced pressor effects of drugs such as adrenaline, isoprenaline, ephedrine and phenylephrine (eg local anaesthetics; nose and eye drops).
Clonidine:	Increased risk of "rebound" hypertension. If used together clonidine should be continued for some time after the beta-blocker has been discontinued.
Insulin and oral hypoglycaemic agents:	Intensify hypoglycaemic effect and mask warning signs of hypoglycaemia (tachycardia)
Anaesthetic agents:	Increased cardio-depressant effect (see *Contra Indications)* but can reduce the risk of dysrhythmias during anaesthesia.
Ergot alkaloids:	Enhanced vasoconstriction.
Antihypertensives:	Enhanced hypotensive effect. Increased risk of first dose hypotension with post-synaptic alpha-blockers such as prazosin.
Moxisylyte (Thymoxamine):	Severe postural hypotension.
Cimetidine and hydralazine:	Increased plasma levels of bisoprolol.

Rifampicin:	Reduced plasma levels of bisoprolol.
Enhanced hypotensive effect with:	Alcohol Alprostadil Antipsychotics (e.g. phenothiazines) Anxiolytics Hypnotics Tricyclic antidepressants Diuretics MAO inhibitors (including risk of hypertensive crisis)
Reduced hypotensive effect with:	NSAIDs/prostaglandin synthetase inhibiting drugs Corticosteroids Oestrogens Combined oral contraceptives

4.6 Pregnancy and lactation

Use with caution in pregnancy especially in the first trimester.

May reduce placental perfusion and cause intrauterine growth retardation/restriction, intrauterine foetal death, immature and premature deliveries.

Use the lowest possible dose and if possible discontinue therapy at least 2 days before delivery to avoid effects on uterine contractility and possible adverse effects (especially bradycardia and hypoglycaemia) in the foetus and neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

Bisoprolol is excreted into breast milk. Breast-feeding is therefore not recommended.

4.7 Effects on ability to drive and use machines

When driving or operating machines it should be taken into account that occasionally dizziness or fatigue may occur. See *Undesirable Effects*.

4.8 Undesirable effects

Blood and Lymphatic Disorders: Thrombocytopenia, purpura.

Psychiatric Disorders: Depression, hallucinations, psychoses, confusion, sleep disturbances, nightmares.

Nervous System Disorders: Fatigue, headaches, impotence, dizziness, paraesthesia of the extremities.

Eye Disorders: Visual disturbances, dry eyes, keratoconjunctivitis.

Cardiac disorders: Bradycardia, slowed AV-conduction or increased existing AV-block, heart failure.

Vascular Disorders: Hypotension, postural hypotension (with syncope), cold and cyanotic extremities, increased existing intermittent claudication, Raynaud's phenomenon.

Respiratory, Thoracic and Mediastinal Disorders: Dyspnoea, bronchospasm.

Gastrointestinal Disorders: Nausea, vomiting, anorexia, diarrhoea, pancreatitis, abdominal pain/discomfort.

Skin and Subcutaneous Tissue Disorders: Allergic rash, urticaria, exacerbation of psoriasis, photosensitivity. Hypersensitivity reactions (such as itching, flush, rash and angioedema)

Reproductive System and Breast Disorders: impotence.

Other: An increase in ANA (antinuclear antibodies) has been seen; its clinical relevance is not clear.

4.9 Overdose

Symptoms of overdosage:

Profound bradycardia, hypoglycaemia, hypotension, acute cardiac insufficiency (heart failure, cardiogenic shock), conduction disorders and possibly cardiac arrest. Also dyspnoea, bronchospasm, impaired consciousness and generalised convulsions may occur.

The onset of symptoms is rapid but effects from a massive overdose may persist for several days despite declining plasma levels.

Treatment:

The patient should be kept under close supervision in intensive care. Gastric lavage, administration of activated charcoal and a laxative will prevent further absorption. Artificial respiration may be required and other emergency measures such as circulatory support or cardiac pacing.

Significant bradycardia or extensive vagal reactions should be treated with intravenous atropine 0.5-2.0mg. Large doses of isoprenaline may be needed for control of heart rate and hypotension or dobutamine. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect, intravenous administration of glucagon (at a dose level of 1 to 5mg) or calcium ions may be considered.

If bronchospasm is treated with a bronchodilator, patients should be monitored for dysrhythmias during and after treatment. For seizures diazepam is the drug of choice.

Patients who recover should be observed for beta-blocker withdrawal phenomenon.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mode of action: Bisoprolol is a potent, highly beta1-selective-adrenoreceptor blocking agent devoid of intrinsic sympathomimetic activity and without relevant membrane stabilising activity.

As with other beta1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma renin activity.

In patients with angina, the blockade of beta1-receptors reduces heart action and thus reduces oxygen demand. Hence bisoprolol is effective in eliminating or reducing the symptoms.

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 plasma elimination 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.

Bisoprolol is effective in hypertension and angina pectoris for at least 24 hours following a single oral dose. The high bioavailability and the dual pathway of clearance lead to predictable blood levels.

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 Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Microcrystalline cellulose; Mannitol; Croscarmellose sodium; Magnesium stearate.

Tablet Coat:

Hypromellose; Titanium dioxide (E171); Macrogol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Blister packs

Do not store above 30^0C. Store in the original package.

Polyethylene bottles

Do not store above 30^oC. Keep the container tightly closed.

6.5 Nature and contents of container

PVC/PVdC-Aluminium Blister packs or polyethylene bottles with polyethylene caps containing 28, 30, 56, 60, 84, 90 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

ACTIVASE PHARMACEUTICALS LIMITED

11 BOUBOULINAS STREET

PO BOX 27783

NICOSIA

2433

CYPRUS

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0006

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