AUSTRALIAN PRODUCT INFORMATION

BICOR®

(bisoprolol fumarate) tablets

1 NAME OF THE MEDICINE

Bisoprolol fumarate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg or 10 mg of bisoprolol fumarate as the active ingredient.

Excipients with known effect: contains sulfites

For the full list of excipients, see 6.1 LIST OF EXCIPIENTS

3 PHARMACEUTICAL FORM

BICOR 1.25 mg (Starter pack):	Round, white, biconvex film-coated tablets
BICOR 2.5 mg:	Heart-shaped, white, biconvex film-coated tablets with a dividing score on both sides
BICOR 3.75 mg:	Heart-shaped, off-white, biconvex film-coated tablets with a dividing score on both sides
BICOR 5 mg:	Heart-shaped, yellowish white, biconvex film-coated tablets with a dividing score on both sides
BICOR 7.5 mg:	Heart-shaped, pale yellow, biconvex film-coated tablets with a dividing score on both sides
BICOR 10 mg:	Heart-shaped, pale orange-light orange, biconvex film-coated tablets with a dividing score on both sides

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of stable chronic moderate to severe heart failure in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

Treatment of CHF consists of an ACE inhibitor (or an angiotensin receptor blocker in case of intolerance to ACE inhibitors), a β-blocker, diuretics, and when appropriate cardiac glycosides.

Patients should be stable (without acute failure) when bisoprolol treatment is initiated.

It is recommended that the treating physician should be experienced in the management of chronic heart failure.

Titration phase

The treatment of stable chronic heart failure with bisoprolol requires a titration phase.

The treatment with bisoprolol is to be started with a gradual uptitration according to the following steps:

- 1.25 mg once daily for 1 week, if well tolerated increase to
- 2.5 mg once daily for a further week, if well tolerated increase to
- 3.75 mg once daily for a further week, if well tolerated increase to
- 5 mg once daily for the 4 following weeks, if well tolerated increase to
- 7.5 mg once daily for the 4 following weeks, if well tolerated increase to
- 10 mg once daily for the maintenance therapy.

The maximum recommended dose is 10 mg once daily.

Close monitoring of vital signs (heart rate, blood pressure), conduction disturbances and symptoms of worsening heart failure is recommended during the titration phase. Symptoms may already occur within the first day after initiating the therapy. Transient worsening of heart failure, hypotension, or bradycardia may occur during titration period and thereafter.

Treatment modification

If the maximum recommended dose is not well tolerated, gradual dose reduction may be considered. In case of transient worsening of heart failure, hypotension, or bradycardia, reconsideration of the dosage of the concomitant medication is recommended. It may also be necessary to temporarily lower the dose of bisoprolol or to consider discontinuation.

The reintroduction and/or uptitration of bisoprolol should always be considered when the patient becomes stable again.

If discontinuation is considered, gradual dose decrease is recommended, since abrupt withdrawal may lead to acute deterioration of the patient's condition.

Treatment of stable chronic heart failure with bisoprolol is generally a long-term treatment.

Method of administration

Bisoprolol tablets should be taken in the morning and can be taken with food. They should be swallowed with liquid and should not be chewed.

Use in hepatic impairment

There is no information regarding the pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

Use in renal impairment

There is no information regarding the pharmacokinetics of bisoprolol in patients with chronic heart failure and with impaired hepatic or renal function. Uptitration of the dose in these populations should therefore be made with additional caution.

4.3 CONTRAINDICATIONS

Bisoprolol is contra-indicated in patients with:

- acute heart failure, episodes of heart failure decompensation requiring i.v. inotropic therapy, cardiogenic shock;
- second or third degree AV block (without a pacemaker);
- sick sinus syndrome or sinoatrial block;
- bradycardia with less than 60 beats/min before the start of therapy;
- 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;
- Raynaud's syndrome;
- untreated phaeochromocytoma (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE);
- metabolic acidosis; and,
- hypersensitivity to bisoprolol or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

The initiation of treatment with bisoprolol necessitates regular monitoring.

There is no therapeutic experience of bisoprolol treatment of heart failure in patients with the following diseases and conditions:

- NYHA class II heart failure
- insulin dependent diabetes mellitus (type 1)
- severely impaired renal function
- severely impaired liver function
- patients older than 80 years
- restrictive cardiomyopathy
- congenital heart disease
- haemodynamically significant organic valvular disease
- myocardial infarction within 3 months

Combination of bisoprolol with calcium antagonists of the verapamil or diltiazem type, with Class I antiarrhythmic drugs and with centrally acting antihypertensive drugs is generally not recommended (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

General anaesthesia

β-blockade reduces the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance β-blockade be continued peri-operatively. The anaesthetist must be made aware of β-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias, attenuation of the reflex tachycardia and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported. Modern inhalational anaesthetic agents are generally well tolerated, although older agents (ether, cyclopropane, methoxyflurane, trichlorethylene) were sometimes associated with severe circulatory depression in the presence of β-blockade. If it is thought necessary to withdraw β-blocker therapy before surgery, this should be done gradually and completed about 48 hours before anaesthesia.

Abrupt withdrawal

The cessation of therapy with bisoprolol should not be done abruptly unless clearly indicated. Care should be taken if β-blockers have to be discontinued abruptly in patients, particularly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias have occurred following abrupt discontinuation of β-blockade in patients with ischaemic heart disease. Therefore, it is recommended that the dosage be reduced gradually over a period of about 8-14 days during which time the patient's progress should be assessed. Bisoprolol should be temporarily reinstituted if the angina worsens markedly or if acute coronary insufficiency develops. If the drug must be withdrawn abruptly,

close observation is required. In the peri-operative period, β-blockers should not be withdrawn unless indicated.

Cardiac failure

There is inadequate evidence of efficacy and safety of bisoprolol treatment in heart failure in patients with NYHA class II heart failure.

Conduction disorders

Very rarely, a pre-existing A-V conduction disorder of moderate degree may become aggravated (possibly leading to A-V block). Bisoprolol should be administered with caution to patients with first degree A-V block (see 4.3 CONTRAINDICATIONS).

Effects on the heart rate

If the patient develops increasing bradycardia (heart rate less than 50 to 55 beats/ minute), the dosage of bisoprolol should be gradually reduced or treatment gradually withdrawn (see 4.3 CONTRAINDICATIONS).

Prinzmetal angina

There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a β-blocker. Cases of coronary vasospasm have been observed. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Peripheral circulation

β-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease. An intensification of complaints may occur, particularly at initiation of therapy (see 4.3 CONTRAINDICATIONS).

Bronchial asthma and chronic obstructive lung disease

Although cardioselective (beta1) beta-blockers may have less effect on lung function than non-selective beta blockers, as with all beta-blockers, these should be avoided in patients with obstructive airways diseases, unless there are compelling clinical reasons for their use. Where such reasons exist bisoprolol may be used with caution. In patients with 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 β_2-stimulants may have to be increased. Bisoprolol is contraindicated in patients with severe bronchial asthma or severe chronic obstructive lung disease.

Diabetes

Bisoprolol should be used with caution in patients with diabetes mellitus, especially those who are receiving insulin or oral hypoglycaemic agents. Diabetic patients should be warned that β-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia.

In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, β-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need adjustment. Such effects on the glucose metabolism may occur with non-selective β-blockers but they are less likely with a β_1-selective agent like bisoprolol. Nevertheless diabetic patients receiving bisoprolol should be monitored to ensure that diabetes control is maintained.

Other metabolic effects

β-adrenoceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some β-blockers affect the lipid profile adversely although the long-term clinical significance of this change is unknown and the effect is more apparent with non-selective β-blockers while it appears to be less for drugs with β_1-adrenoceptor-selectivity and for those with intrinsic sympathomimetic activity.

Thyrotoxicosis

Under treatment with bisoprolol the symptoms of thyrotoxicosis may be masked.

Phaeochromocytoma

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

Allergic conditions

As with other β-blockers, bisoprolol may increase both the sensitivity towards allergens and the severity of anaphylactic reactions. Adrenaline (epinephrine) treatment does not always give the expected therapeutic effect.

Psoriasis

Patients with psoriasis, or with a history of psoriasis, should only be given β-blockers after carefully balancing the benefits against the risks.

Effects on the eye and skin

Various rashes and conjunctival xeroses have been reported with β-blocking agents. Cross reactions may occur between β-blockers, therefore substitutions within the group may not necessarily preclude occurrence of symptoms.

Strict Fasting

Bisoprolol must be used with caution in patient undergoing strict fasting.

Use in hepatic impairment

Caution is advised in patients with CHF and impaired hepatic function since there is no information regarding pharmacokinetics in these patients. Renal function should be monitored in patients with severe liver disease. Renal impairment may develop in patients with liver disease during bisoprolol treatment, leading to a need for dose reduction.

Use in renal impairment

No dosage adjustment is required in patients with impairment of the kidney due to excretion equally by both liver and kidney. Nevertheless, caution is advised since there is no information regarding pharmacokinetics in CHF patients.

Use in the Elderly

Based on age alone no dosage adjustments are required; however, caution is advised in patients greater than 80 years old since data in this age group is limited (see 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric use

The safety and efficacy in children have not been established.

There is no paediatric experience with bisoprolol; therefore, its use cannot be recommended for children.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

General

The clearance of bisoprolol is 'balanced' between renal elimination of the unchanged drug and hepatic metabolism, renal clearance accounting for at least 50% of the dose. The remainder is subject to metabolism

primarily by CYP3A4, with a minor contribution from CYP2D6. Bisoprolol plasma concentrations are expected to increase during concurrent administration of CYP3A4 inhibitors by not more than a factor of 2, and decrease during concurrent administration of CYP3A4 inducers. Due to the minor role of CYP2D6 in bisoprolol metabolism, CYP2D6 inhibitors and genetic differences in CYP2D6 activity do not significantly alter bisoprolol plasma concentrations. Bisoprolol may increase the plasma concentrations of other drugs metabolised by CYP3A4 and possibly those metabolised by CYP2D6.

Combinations not recommended

Calcium antagonists of the verapamil type and to a lesser extent of the diltiazem type: Negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients on β-blocker treatment may lead to profound hypotension and atrioventricular block.

Class I antiarrhythmic drugs (e.g. quinidine, disopyramide; lidocaine, phenytoin; flecainide, propafenone): Effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased.

Centrally acting antihypertensive drugs such as clonidine and others (e.g. methyldopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation). Abrupt withdrawal, particularly if prior to β-blocker discontinuation, may increase risk of "rebound hypertension".

Combinations to be used with caution

Calcium antagonists of the dihydropyridine type such as felodipine and amlodipine: 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.

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

Topical β-blockers (e.g. eye drops for glaucoma treatment) may add to the systemic effects of bisoprolol.

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

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

General anaesthetics. β-blockade reduces the incidence of arrhythmias and myocardial ischaemia during induction and intubation, and the post-operative period. It is currently recommended that maintenance β-blockade be continued peri-operatively. The anaesthetist must be made aware of β-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias, attenuation of the reflex tachycardia and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia (see 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE – GENERAL ANAESTHESIA).

Digitalis glycosides: Reduction of heart rate, increase of atrio-ventricular conduction time.

Non-steroidal anti-inflammatory drugs (NSAIDs): NSAIDs may reduce the hypotensive effect of bisoprolol.

β-Sympathomimetic agents (e.g. isoprenaline, dobutamine): Combination with bisoprolol may reduce the effect of both agents.

Sympathomimetics that activate both β- and α-adrenoceptors (e.g. noradrenaline, adrenaline (epinephrine)): Combination with bisoprolol may unmask the α-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 β-blockers.

Higher doses of adrenaline (epinephrine) may be necessary for treatment of allergic reactions.

Concomitant use with antihypertensive agents as well as with other drugs with blood pressure lowering potential (e.g. tricyclic antidepressants, barbiturates, phenothiazines) may increase the risk of hypotension.

Combinations to be considered

Mefloquine: increased risk of bradycardia

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

Ergotamine derivatives: Exacerbation of peripheral circulatory disturbances.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No effect on fertility was observed in male or female rats treated with bisoprolol at oral doses up to 150 mg/kg/day (associated with bisoprolol plasma concentrations (AUC) about 50 times those expected in humans after daily doses of 10 mg bisoprolol).

Use in pregnancy (Category C)

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 fetal 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.

Studies in rats have shown that bisoprolol and/or its metabolites cross the placenta and distribute to the foetus.

Administration of bisoprolol at oral doses of ≥50 mg/kg/day to pregnant rats or ≥12.5 mg/kg/day to pregnant rabbits caused embryofoetal toxicity, resorptions and abortions. The no-effect dose for embryofoetal toxicity and mortality was 40 mg/kg/day (associated with plasma drug concentrations (AUC) 11 times that expected in humans after 10 mg/kg/day bisoprolol) for rats and 10 mg/kg/day for rabbits (associated with AUC lower than that expected in humans after 10 mg/kg/day doses). No evidence for teratogenic effects of bisoprolol was observed at any dose in rats or rabbits.

Use in lactation

Bisoprolol and/or its metabolites have been found in the milk of lactating rats.

Treatment of rats with bisoprolol at oral doses of 150 mg/kg/day from late gestation and during the lactation period was associated with decreased offspring birthweight and retarded physical development. The no-effect dose (50 mg/kg) for these effects was associated with an AUC *ca* 14 times greater than that expected in humans.

There are no data on the excretion of bisoprolol in human breast milk or the safety of bisoprolol exposure in infants. Therefore, breastfeeding is not recommended during administration of bisoprolol.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Bisoprolol may cause dizziness or fatigue (see 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and, therefore, may adversely affect the patient's ability to drive or use machinery. In a study with 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 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The table below shows incidences of adverse events reported from both the placebo and the bisoprolol cohort of the CIBIS II trial. Regardless of causal relationship all adverse events are included. Each patient is only counted once for each adverse event occurring in at least 1 % of the study population.

Preferred Term WHO	Placebo (n=1321)		Bisoprolol (n=1328)	
	Patients with AE	% Patients with AE	Patients with AE	% Patients with AE
Cardiac failure	301	22.8	244	18.4
Dyspnoea	224	17.0	183	13.8
Dizziness	126	9.5	177	13.3
Cardiomyopathy	132	10.0	141	10.6
Bradycardia	60	4.5	202	15.2
Hypotension	96	7.3	152	11.4
Tachycardia	144	10.9	79	5.9
Fatigue	94	7.1	123	9.3
Viral infection	75	5.7	86	6.5
Pneumonia	69	5 2	65	4.9
Hypertension	71	5.4	58	4.4
Bronchitis	75	5.7	53	4.0
Arrhythmia	78	5.9	49	3.7
Coughing	65	4.9	56	4.2
Dyspepsia	58	4.4	63	4.7
Peripheral oedema	54	4.1	58	4.4
Chest pain	54	4.1	54	4.1
Headache	57	4.3	49	3.7
Purine metabolism disorder	46	3.5	55	4.1
Carbohydrate metabolism disturbed	43	3.3	49	3.7
Ischaemia	29	2.2	57	4.3
Exertional dyspnoea	50	3.8	35	2.6
Conduction disorder	41	3.1	41	3.1
Upper resp. tract infection	50	3.8	28	2.1
Nausea	35	2.6	42	3.2
Asthenia	34	2.6	42	3.2
Oedema	39	3.0	33	2.5
Left cardiac failure	36	2.7	32	2.4
Pain in limbs	37	2.8	31	2.3
Cerebrovascular disorder	27	2.0	36	2.7
Weight changes	30	2.3	33	2.5
Arthralgia	34	2.6	28	2.1
Syncope	27	2.0	29	2.2

Preferred Term WHO	Placebo (n=1321)		Bisoprolol (n=1328)	
	Patients with AE	% Patients with AE	Patients with AE	% Patients with AE
Insomnia	23	1.7	25	1.9
Body pain	25	1.9	19	1.4
Epigastric pain not food-related	23	1.7	20	1.5
Abdominal pain	19	1.4	22	1.7
Cholesterol changes	20	1.5	21	1.6
Depression	25	1.9	16	1.2
Respiratory distress	19	1.4	20	1.5
Constipation	21	1.6	17	1.3
Palpitation	19	1.4	18	1.4
Hepatomegaly	21	1.6	15	1.1
Stridor	18	1.4	18	1.4
Vein disorder	22	1.7	12	0.9
Urinary tract infection	20	1.5	13	1.0
Respiratory tract oedema	19	1.4	13	1.0
Fever	11	0.8	21	1.6
Myalgia	14	1.1	17	1.3
Potassium levels altered	18	1.4	13	1.0
Anxiety	21	1.6	9	0.7
Gastritis	13	1.0	17	1.3
Arthropathy	9	0.7	18	1.4
Blood lipids changes	11	0.8	16	1.2
Fractures	14	1.1	13	1.0
Malaise	9	0.7	18	1.4
Pruritus	10	0.8	15	1.1
Respiratory tract hemorrhage	15	1.1	10	0.8

AE = Adverse Events

Post-marketing data

The following definitions apply to the frequency terminology used hereafter:

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)

Investigations:

Rare: increased triglycerides, increased liver enzymes (ALT, AST).

Cardiac disorders:

Very common: bradycardia

Common: worsening of pre-existing heart failure

Uncommon: AV-conduction disturbances

Nervous system disorders:

Common: dizziness, headache.

Eye disorders:

Rare: reduced tear flow (to be considered if the patient uses lenses).

Very rare: conjunctivitis.

Ear and labyrinth disorders:

Rare: hearing disorders.

Respiratory, thoracic and mediastinal disorders:

Uncommon: bronchospasm in patients with bronchial asthma or a history of obstructive airways disease.

Rare: allergic rhinitis.

Gastrointestinal disorders:

Common: gastrointestinal complaints such as nausea, vomiting, diarrhoea, constipation.

Skin and subcutaneous tissue disorders:

Rare: hypersensitivity reactions (pruritus, flush, rash and angioedema).

Very rare: alopecia, β-blockers may provoke or worsen psoriasis or induce psoriasis-like rash..

Musculoskeletal and connective tissue disorders:

Uncommon: muscular weakness and cramps.

Vascular disorders:

Common: feeling of coldness or numbness in the extremities, hypotension.

Uncommon: orthostatic hypotension.

Frequency not known: syncope

General disorders:

Common: asthenia, fatigue.

Hepatobiliary disorders:

Rare: hepatitis.

Reproductive system and breast disorders:

Rare: erectile dysfunction.

Psychiatric disorders:

Uncommon: sleep disorders, depression.

Rare: nightmares, hallucinations.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The most common signs expected with overdosage of a β-blocker are bradycardia, hypotension, bronchospasm, acute cardiac insufficiency and hypoglycaemia. There is limited experience with overdose of bisoprolol, only a few cases of overdose with bisoprolol have been reported. Bradycardia and/or hypotension were noted. All patients recovered. There is a wide interindividual variation in sensitivity to one single high dose of bisoprolol and patients with heart failure are probably very sensitive.

In general, if overdose occurs, discontinuation of bisoprolol treatment and supportive and symptomatic treatment is recommended.

Based on the expected pharmacologic 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 temporary pacing.

Acute worsening of heart failure: Administer i.v. diuretics, inotropic agents, vasodilating agents.

Bronchospasm: Administer bronchodilator therapy such as isoprenaline, β2-sympathomimetic drugs and/or aminophylline.

Hypoglycaemia: Administer i.v. glucose.

Limited data suggest that bisoprolol is hardly dialyzable.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Bisoprolol is a β1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows very low affinity to the β2-receptor of the smooth muscles of bronchi and vessels as well as to the β2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and β2-mediated metabolic effects. Its β1-selectivity extends beyond the therapeutic dose range. However, its β1-selectivity is not absolute and at doses greater than the maximum recommended of 10 mg, bisoprolol may also inhibit β2-adrenoreceptors.

The haemodynamic effects of bisoprolol are those that can be expected from β-adrenoceptor blockade. Besides the negative chronotropic effect resulting in a reduction in resting and exercise heart rate there is, as shown in acute studies with iv administration, a fall in resting and exercise cardiac output with only little change in stroke volume, and a small increase in right atrial pressure at rest or during exercise. The decrease in cardiac output correlates with the heart rate reduction, and the observed increases in total peripheral resistance and pulmonary arterial resistance after acute administration are considered to be due to reflex autonomic changes resulting from the negative chronotropic and slight negative inotropic effects.

Acute iv administration of 10 mg bisoprolol to hypertensive patients reduced glomerular filtration rate (GFR), renal blood flow (RBF) and plasma renin activity (PRA) whereas the renal vascular resistance was reduced after short-term treatment (10 mg bisoprolol po for 4 weeks) with no significant changes in RBF, GFR or

PRA. Epinephrine and norepinephrine levels also remained unaffected after the 4-week treatment in hypertensive patients.

Bisoprolol shows the same pattern of cardiac electrophysiologic effects as other β-adrenoceptor blocking agents. It acts on those parts of the conduction system that are influenced by the sympathetic nervous system. In electrophysiological studies it reduced heart rate, prolonged SA and AV nodal conduction, and prolonged the refractory periods of the SA and AV node. There was no statistically significant effect on atrial effective refractory period in patients with a history of syncope or cardiac arrhythmias. However, in patients with coronary artery disease, there was a small significant increase in right atrial effective and functional refractory periods. Right ventricular effective refractory period was temporarily prolonged during a study in patients with coronary artery disease, but the clinical relevance of the small increase is uncertain. RR and PR intervals were increased and QTc intervals reduced but all parameters remained within normal limits after bisoprolol.

Clinical trials

In total 2647 ambulatory patients with chronic heart failure were included in the CIBIS II trial in accordance with the following inclusion/exclusion criteria:

Inclusion criteria: CHF of at least three months duration (stable for at least 6 weeks).

Exclusion criteria: Resting heart rate <60 beats/min; supine systolic BP <100 mmHg; myocardial infarction or unstable angina within the preceding 3 months; PTCA or CABG within the preceding 6 months; atrioventricular block of second degree or greater without a functioning pacemaker, haemodynamically significant organic valvular disease; obstructive or restrictive cardiomyopathy.

83% (n = 2202) of patients were in NYHA class III and 17% (n = 445) were in NYHA class IV. They had stable symptomatic systolic heart failure (ejection fraction ≤ 35%, based on echocardiography). Total mortality was reduced from 17.3% to 11.8% (absolute reduction 5.5%; relative reduction 34% [95% confidence interval 19-46%]).

A decrease in sudden death (3.6% vs. 6.3%, relative reduction 44%) and a reduced number of heart failure episodes requiring hospital admission (12% vs 17.6%, relative reduction 36%) was observed. Finally, a significant improvement of the functional status according to NYHA classification has been shown. During the initiation and titration of bisoprolol hospital admissions due to bradycardia (0.53%), hypotension (0.23%), and acute decompensation (4.97%) were observed, but they were not more frequent than in the placebo-group (0%, 0.3% and 6.74%).

5.2 PHARMACOKINETIC PROPERTIES

Absorption.

Bisoprolol is almost completely (>90%) absorbed from the gastrointestinal tract and, because of its small first pass metabolism of about 10%-15%, has an absolute bioavailability of about 85-90% after oral administration. The bioavailability is not affected by food. The drug shows linear kinetics and the plasma concentrations are proportional to the administered dose over the dose range 5 to 20 mg. Peak plasma concentrations occur within 2-3 hours.

Distribution.

Bisoprolol is extensively distributed. The volume of distribution is 3.5 L/kg. Binding to plasma proteins is approximately 35%; uptake into human blood cells was not observed.

Metabolism.

In humans, only oxidative metabolic pathways have been detected with no subsequent conjugation. All metabolites, being very polar, are renally eliminated. The major metabolites in human plasma and urine were found to be without pharmacological activity. *In vitro* data from studies in human liver microsomes show that bisoprolol is primarily metabolized via CYP3A4 (~95%) with CYP2D6 having only a minor role. The minor contribution of CYP2D6 to the metabolism of bisoprolol observed *in vitro* is consistent with the *in vivo* data in extensive and restricted debrisoquine metabolisers, which showed no difference between the two groups of

metabolisers. Bisoprolol is a racemate consisting of the R and S enantiomers. The intrinsic clearance by human recombinant CYP3A4 appears to be non-stereoselective while the metabolism by CYP2D6 is stereoselective (R/S =1.50).

Excretion.

The clearance of bisoprolol is 'balanced' between renal elimination of the unchanged drug (~50%) and hepatic metabolism (~50%) to metabolites which are also renally excreted. The total clearance of the drug is 15.6 ± 3.2 L/h with renal clearance being 9.6±1.6 L/h. In a study with 14C-labelled bisoprolol the total urinary and fecal excretion was 90 ± 2.7% and 1.4 ± 0.1% of the dose, respectively (mean ± SEM recoveries of the total dose within 168 hours). Bisoprolol has an elimination half-life of 10-12 hours.

Renal Impairment. Since the clearance of bisoprolol is balanced between renal and hepatic mechanisms, the plasma accumulation factor of bisoprolol in patients with either complete renal or hepatic impairment should not exceed 2. In a study in patients with a mean creatinine clearance of 28 mL/min, the plasma accumulation factor was less than 2, and it has been shown that as the creatinine clearance falls the AUC increases as does the $t_{½}$ and C_{max}. According to these studies in patients with renal impairment no dosage adjustment is normally required up to the maximum dose of 10 mg bisoprolol.

Hepatic Impairment . There were no clinically relevant differences in the pharmacokinetics of bisoprolol between patients with normal or impaired hepatic function. Thus, dose reduction is not required in patients with liver disease. Renal function should be monitored in patients with severe liver disease, since renal impairment may develop and require dose reduction.

Chronic Cardiac Failure. In a small substudy of the CIBIS II study in patients with CHF (NYHA III) on 10 mg bisoprolol, the steady state AUC was greater, the $t_{½}$ longer (17±5 hours) and the clearance lower than in healthy volunteers, the values being similar to those observed in patients with renal impairment. Bisoprolol pharmacokinetics in patients with CHF and concomitant impaired liver and/or renal function have not been studied, however dose reduction may be required in such patients.

Elderly. Some pharmacokinetic parameters ($t_{½}$, AUC, C_{max}) have been found to be greater in the elderly compared to those in the young which appears to be due to a reduction in renal clearance in the elderly. However, the pharmacokinetic differences between the young and the elderly are unlikely to be clinically significant, and based on age alone no dosage adjustments are required.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence for genotoxic activity was observed with bisoprolol in *in vitro* assays of gene mutation (reverse mutation in *Salmonella typhimurium*, forward mutation in Chinese hamster V79 fibroblasts) or chromosomal damage (CHO cytogenetic assay). Negative findings were also obtained with bisoprolol in *in vivo* assays of chromosomal damage (Chinese hamster bone marrow cytogenetic assay and the mouse micronucleus test).

Carcinogenicity

Bisoprolol showed no evidence of carcinogenic activity when administered orally (via the diet) to mice for 20-26 months at doses up to 250 mg/kg/day and to rats for 24 months at doses up to 125 mg/kg/day. These doses were associated with plasma drug concentrations (AUC) 38 times (mice) or 15 -18 times (rats) greater than those expected in humans after 10 mg/day of bisoprolol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BICOR tablet contain colloidal anhydrous silica, magnesium stearate, crospovidone, maize starch, microcrystalline cellulose, calcium hydrogen phosphate, dimeticone 100, macrogol 400, titanium dioxide and hypromellose.

BICOR 1.25 mg tablets also contain pregelatinized maize starch and purified talc.

BIICOR 3.75 mg, 5 mg, 7.5 mg and 10 mg tablets also contain iron oxide yellow. BICOR 10 mg tablets also contain iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging

6.4 SPECIAL PRECAUTIONS FOR STORAGE

BICOR 1.25 mg (Starter pack), 2.5 mg, 3.75 mg: Store below 25°C.

BICOR 5 mg, 7.5 mg, 10 mg: Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/Al

Pack size: 7, 10, 28, 30, 42, 56, 100 tablets (1.25 mg starter pack, 2.5 mg, 3.75 mg, 5 mg strengths)

10, 28, 30, 42, 56, 100 tablets (7.5 mg, 10 mg strengths)

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 81603 - BICOR bisoprolol fumarate 1.25 mg tablet blister pack

AUST R 81604 - BICOR bisoprolol fumarate 2.5 mg tablet blister pack

AUST R 81605 - BICOR bisoprolol fumarate 3.75 mg tablet blister pack

AUST R 81606 - BICOR bisoprolol fumarate 5 mg tablet blister pack

AUST R 81607 - BICOR bisoprolol fumarate 7.5 mg tablet blister pack

AUST R 81608 - BICOR bisoprolol fumarate 10 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

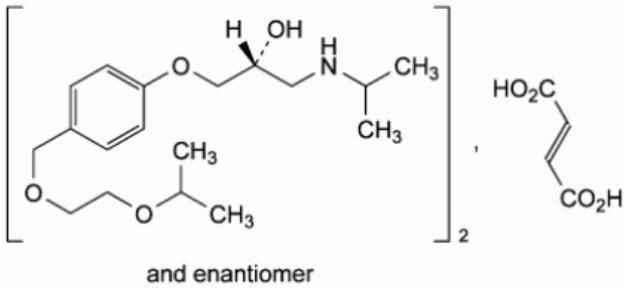
6.7 PHYSICOCHEMICAL PROPERTIES

Bisoprolol fumarate is a white crystalline substance with a melting range of 100-104°C. It is very soluble in water and methanol, freely soluble in ethanol, glacial acetic acid and chloroform. As the substance is present in the form of a racemate, the aqueous solution does not show optical activity. With the underlying manufacturing conditions no polymorphic forms were observed.

Chemical structure

Chemical name:
(*RS*)-1-[4-[[2-(1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]propan-2-ol fumarate

Structural formula:



Molecular formula: $C_{40}H_{66}N_2O_{12}$
Molecular weight: 767

CAS number

104344-23-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

02/02/2007

10 DATE OF REVISION

04/07/2024

Summary table of changes

Section Changed	Summary of new Information
All	Minor editorial changes
2, 3	Minor editorial changes to tablet details and description
6.1	Minor editorial changes to excipient details
6.4	Minor editorial changes to storage details
6.5	Minor editorial changes to container details and inclusion of AUST R details
8	Update to Sponsor details

BICOR® is licenced to the Viatris company group

BICOR_pi\Jul24/00