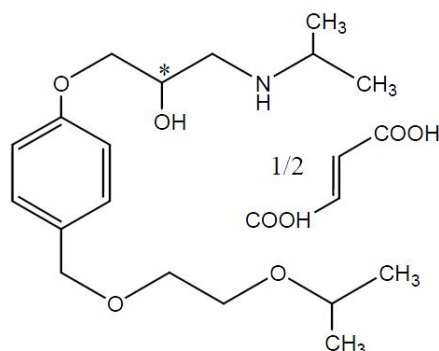


APO-BISOPROLOL TABLETS**NAME OF THE MEDICINE****BISOPROLOL FUMARATE**

Chemical Name: (±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl]oxy]-3-isopropylamino-2-propanol hemifumarate

Structural Formula:



Molecular Formula: $C_{18}H_{31}NO_4 \cdot \frac{1}{2}C_4H_4O_4$

Molecular Weight: 383.49

CAS Registry Number: 104344-23-2

DESCRIPTION

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.

Each tablet contains 1.25 mg, 2.5 mg, 3.75 mg, 5 mg or 10 mg of Bisoprolol fumarate.

In addition, each tablet contains the following inactive ingredients:

Microcrystalline cellulose, silica colloidal anhydrous, croscarmellose sodium, sodium starch glycollate (type A) and magnesium stearate.

PHARMACOLOGY**Pharmacological Action**

Bisoprolol is a β_1 -selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows very low affinity to the β_2 -receptor of the smooth muscles of bronchi and vessels as well as to the β_2 -receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and β_2 -mediated metabolic effects. Its β_1 -selectivity extends beyond the therapeutic dose range. However, its β_1 -selectivity is not absolute and at doses greater than the maximum recommended of 10mg, bisoprolol may also inhibit β_2 -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 intravenous 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 intravenous administration of 10mg 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 (10mg bisoprolol per os for 4 weeks) with no significant changes in RBF, GFR or PRA. Adrenaline (epinephrine) and noradrenalin (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 sinoatrial (SA) and atrioventricular (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.

Pharmacokinetics

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 20mg. Peak plasma concentrations occur within 2-3 hours.

Following oral administration of bisoprolol fumarate 10mg to healthy subjects under fasting conditions, a mean peak plasma concentration (C_{max}) of Bisoprolol of approximately 31.86 ng/mL was achieved within approximately 2 hours (T_{max}).

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 ^{14}C -labelled bisoprolol the total urinary and fecal excretion was $90 \pm 2.7\%$ and $1.4 \pm 0.1\%$ of the dose, respectively (mean \pm 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 accumulation 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 accumulation was less than 2, and it has been shown that as the creatinine clearance falls the AUC increases as does the $t_{1/2}$ and C_{max} . According to these studies in patients with renal impairment no dosage adjustment is normally required up to the maximum dose of 10mg 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 10mg bisoprolol, the steady state AUC was greater, the $t_{1/2}$ 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 ($t_{1/2}$, 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.

CLINICAL TRIALS

In total 2,647 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; percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (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 $\leq 35\%$, 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%).

INDICATIONS

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

CONTRAINDICATIONS

Bisoprolol is contra-indicated in patients with:

- acute heart failure, episodes of heart failure decompensation requiring intravenous inotropic therapy, cardiogenic shock;
- AV block of second or third degree (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 pheochromocytoma (see PRECAUTIONS);
- metabolic acidosis;

- hypersensitivity to bisoprolol or to any of the excipients.

PRECAUTIONS

Use with caution in the following circumstances

The initiation of treatment with bisoprolol necessitates regular monitoring.

There is no therapeutic experience of bisoprolol treatment in insulin dependent diabetes mellitus (type 1), impaired renal function (serum creatinine $\geq 300 \mu\text{mol/l}$), impaired liver function, patients older than 80 years, restrictive cardiomyopathy, congenital heart disease, haemodynamically significant organic valvular disease and 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 Interactions with Other Medicines)

General anaesthetics: Beta-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 medicines, 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 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 no therapeutic experience of bisoprolol treatment in heart failure in patients with NYHA class II heart failure.

Conduction disorders: Very rarely, a pre-existing AV conduction disorder of moderate degree may become aggravated (possibly leading to AV block). Bisoprolol should be administered with caution to patients with first degree AV block (see 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 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. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

Peripheral circulation: Beta-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 CONTRAINDICATIONS).

Bronchial asthma and chronic obstructive lung disease: 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 beta-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. Beta-adrenoceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some beta-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 beta-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.

Renal disease: 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.

Liver disease: 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.

Allergic conditions: 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.

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.

Effects on ability to drive or use machinery: Bisoprolol may cause dizziness or fatigue (see ADVERSE 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.

Fasting: Bisoprolol should be used with caution in patients under strict fasting conditions.

Effects on Fertility

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

Use in Pregnancy (Category C)

Bisoprolol has pharmacological effects that may cause harmful effects on pregnancy and/or the fetus/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 fetus 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 fetus 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 fetus.

Administration of bisoprolol at oral doses of ≥ 50 mg/kg/day to pregnant rats or ≥ 12.5 mg/kg/day to pregnant rabbits caused embryofetal toxicity, resorptions and abortions. The no-effect dose for embryofetal 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 birth weight and retarded physical development. The no-effect dose (50 mg/kg) for these effects was associated with an AUC about 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.

Paediatric Use

The safety and efficacy in children have not been established.

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 Pharmacology – Pharmacokinetics).

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.

INTERACTIONS WITH OTHER MEDICINES

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. methyl dopa, moxonidine, rilmenidine): Concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tone (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: Beta-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 medicines, 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 Precautions – General Anaesthesia).

Digitalis glycosides: Reduction of heart rate, increase of atrioventricular 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): 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 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:

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.

Mefloquine: increased risk of bradycardia.

ADVERSE EFFECTS**Clinical trials 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	183	13.8
Dizziness	126	9.5	177	13.3
Cardiomyopathy	132	10	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
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	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
Asthenia	34	2.6	42	3.2
Oedema	39	3	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	36	2.7
Weight changes	30	2.3	33	2.5
Arthralgia	34	2.6	28	2.1
Syncope	27	2	29	2.2

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
Respiratory tract oedema	19	1.4	13	1
Fever	11	0.8	21	1.6
Myalgia	14	1.1	17	1.3
Potassium levels altered	18	1.4	13	1
Anxiety	21	1.6	9	0.7
Gastritis	13	1	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
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 ($\geq 1/10$)

Common ($\geq 1/100$, $< 1/10$)

Uncommon ($\geq 1/1,000$, $< 1/100$)

Rare ($\geq 1/10,000$, $< 1/1,000$)

Very rare ($< 1/10,000$)

Investigations:

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

Cardiac disorders:

Very common: bradycardia.

Common: worsening of heart failure.

Uncommon: AV-conduction disturbances.

Nervous system disorders:

Common: 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.

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 (itching, flush, rash).

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

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.

General disorders:

Common: asthenia, fatigue*.

Hepatobiliary disorders:

Rare: hepatitis.

Reproductive system and breast disorders:

Rare: potency disorders.

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

DOSAGE AND ADMINISTRATION

Treatment of chronic heart failure consists of an ACE inhibitor (or 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:

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

The maximum recommended dose is 10mg 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 patients condition.

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

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.

Special population:

Use in patients with hepatic or renal impairment:

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

Infants and Children

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

Use in the Elderly

No dosage adjustment is required.

OVERDOSAGE

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 intravenous diuretics, inotropic agents, vasodilating agents.

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

Hypoglycaemia: Administer intravenous glucose.

Limited data suggest that bisoprolol is hardly dialyzable.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

APO-BISOPROLOL 1.25 mg tablets AUST R 182108

1.25 mg: A white to off white, round, biconvex tablet, debossed '1.25' and plain on the other side

APO-BISOPROLOL 2.5 mg tablets AUST R 182106

2.5 mg: A white to off white, round, biconvex tablet, debossed '2' bisect '5' and plain on the other side

APO-BISOPROLOL 3.75 mg tablets AUST R 182117

3.75 mg: A white to off white, round, biconvex tablet, debossed '3.75' and plain on the other side

APO-BISOPROLOL 5 mg tablets AUST R 182114

5 mg: A white to off white, round, biconvex tablet, debossed '5' on the left of a break line and plain on the other side

APO-BISOPROLOL 10 mg tablets AUST R 182123

10 mg: A white to off white, round, biconvex tablet, debossed '10' on the left of a break line and plain on the other side

Blister packs of 7, 10, 28, 30, 42, 56 and 100 tablets

* Not all strengths, pack types and/or pack sizes may be available.

APO-BISOPROLOL TABLETS are/is intended for oral administration. Each tablet contains 1.25 mg, 2.5 mg, 3.75 mg, 5 mg or 10 mg of Bisoprolol fumarate.

In addition, each tablet contains the following inactive ingredients :

Microcrystalline cellulose, silica colloidal anhydrous, croscarmellose sodium, sodium starch glycollate (type A) and magnesium stearate.

Storage

Store below 25°C.

Protect from light

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

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