PRODUCT MONOGRAPH

APO-BISOPROLOL

Bisoprolol Fumarate Tablets USP

5 mg, 10 mg

β-adrenoceptor blocking agent

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Bisoprolol Fumarate Tablets USP 5 and 10 mg

PHARMACOLOGICAL CLASSIFICATION
β-adrenoceptor blocking agent

ACTION AND CLINICAL PHARMACOLOGY

Bisoprolol fumarate is a synthetic β_1-selective (cardioselective) adrenoceptor blocking agent without significant membrane stabilizing activity or intrinsic sympathomimetic activity in its therapeutic dosage range. This preferential effect is not absolute, however, and at higher doses bisoprolol may also inhibit β_2-adrenoceptors, located chiefly in the bronchial and vascular musculature.

Pharmacodynamics

The most prominent effect of bisoprolol is the negative chronotropic effect, resulting in a reduction in resting and exercise heart rate. There is a fall in resting and exercise cardiac output with little observed change in stroke volume, and only a small increase in right atrial pressure, or pulmonary capillary wedge pressure at rest or during exercise.

The mechanism of action of its antihypertensive effects has not been completely established. Factors which may be involved include:
1) Antagonism of β-adrenoceptors to decreased cardiac output

2) Inhibition of renin release by the kidneys

3) Diminution of tonic sympathetic outflow from the vasomotor centers in the brain

In normal volunteers, bisoprolol therapy resulted in a reduction of exercise and isoproterenol-inducted tachycardia. The maximal effect occurred with 1 -4 hours post-dosing. Effects persisted for 24 hours at doses equal to or greater than 5 mg.

Electrophysiology studies in man have demonstrated that bisoprolol significantly decreases heart rate, increases sinus node recovery time, prolongs AV node refractory periods, and with rapid atrial stimulation, prolongs AV nodal conduction.

Bisoprolol fumarate is well absorbed following oral administration. The absolute bioavailability after a 10 mg dose is greater than 80%. Absorption is not affected by the presence of food. The first pass metabolism of bisoprolol fumarate is less than 20%.

Binding to serum proteins is approximately 30%. Peak plasma concentrations occur within 2 - 4 hours of dosing with 5 to 20 mg, and mean peak values range from 16 ng/mL to 5 mg to 70 ng/mL at 20 mg. Once daily dosing with bisoprolol fumarate results in less than two fold intersubject variation in peak plasma levels. The plasma elimination half-life is 9 - 12 hours and is slightly longer in elderly patients in part

because of decreased renal function in that population. Steady-state is attained within 5 days with once-daily dosing. In both young and elderly populations, plasma accumulation is low; the accumulation factor ranges from 1.1 to 1.3, and is what would be expected from the first order kinetics and once-daily dosing. Plasma concentrations are proportional to administered dose in the range of 5 to 20 mg. Pharmacokinetic characteristics of the two enantiomers are similar.

Bisoprolol fumarate is eliminated equally by renal and non-renal pathways with about 50% of the dose appearing unchanged in the urine and the remainder appearing in the form of inactive metabolites. In humans, the known metabolites are labile or have no known pharmacologic activity. Less than 2% of the dose is excreted in the feces. Bisoprolol fumarate is not metabolized by cytochrome P450 II D6 (debrisoquin hydroxylase).

In subjects with creatinine clearance less than 40 mL/min, the plasma half-life is increased approximately three-fold compared to healthy subjects.

In patients with liver cirrhosis, the rate of elimination of bisoprolol fumarate is more variable and significantly slower than that in healthy subjects, with plasma half-life ranges from 8.3 to 21.7 hours.

COMPARATIVE BIOAVAILABILITY

A comparative bioavailability study was performed on healthy human volunteers under fasting conditions. The rate and extent of absorption of bisoprolol fumarate was measured and compared following a single oral dose of APO-BISOPROLOL (bisoprolol fumarate) or MONOCOR® tablets. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data for a Single-Dose Fasting Study of Bisoprolol Fumarate (1x10 mg) Tablets

Bisoprolol (1x10 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Apo-Bisoprolol	Monoco®†	% Ratio of Geometric Means	90% Confidence Interval
AUCT (ng.h/ml)	604 614 (19)	609 619 (19)	98.9	95.6-102.2
AUC1 (ng.h/ml)	634 646 (20)	639 651 (20)	98.8	95.4-102.4
C_{MAX} (ng/ml)	39.4 40.2 (20)	39.4 40.1 (18)	99.7	94.6-105.1
*T_{MAX} (h)	3.30 (63)	2.75 (47)		
*T(h)	10.7 (15)	10.8 (15)		

*expressed as the arithmetic mean (CV%) only.

†Monocor® manufactured by Biovail Pharmaceuticals was purchased in Canada.

INDICATIONS AND CLINICAL USAGE

APO-BISOPROLOL (bisoprolol fumarate) is indicated in the management of patients with mild to moderate hypertension. It may be used alone or in combination with other antihypertensive agents, particularly thiazide diuretics.

APO-BISOPROLOL is not recommended for the emergency treatment of hypertensive crisis.

CONTRAINDICATIONS

APO-BISOPROLOL (bisoprolol fumarate) is contraindicated in patients with cardiogenic shock, overt heart failure, second or third degree A-V block, right ventricular failure secondary to pulmonary hypertension, and sinus bradycardia.

WARNINGS

Cardiac Failure:

Special caution should be exercised when administering APO-BISOPROLOL (bisoprolol fumarate) to patients with a history of severe heart failure. Safety and effectiveness of bisoprolol doses higher than 10 mg per day in patients with heart failure have not been established. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. In general, β-blocking agents should be avoided in patients with overt congestive failure.

However, in some patients with compensated cardiac failure, it may be necessary to utilize them. In such a situation, they must be used cautiously. APO-BISOPROLOL acts selectively without abolishing the effects of digitalis. However, the positive inotropic effect of digitalis may be reduced by the negative inotropic effect of APO-BISOPROLOL when the two drugs are used concomitantly. The effects of β-blockers and digitalis are additive in depressing A-V conduction.

Patients Without a History of Cardiac Failure:

In patients without a history of cardiac failure continued depression of the myocardium with β- blockers in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be treated appropriately and the response observed closely. If cardiac failure continues, APO-BISOPROLOL therapy should be immediately withdrawn.

Abrupt Cessation of Therapy with APO-BISOPROLOL:

Exacerbation of angina pectoris, and, in some instances, myocardial infarction or ventricular arrhythmia, have been observed in patients with coronary artery disease following abrupt cessation of therapy with β-blockers. Patients should, therefore, be cautioned against interruption or discontinuation of therapy without the physician's advice. Even in patients without overt coronary artery disease, it may be advisable to taper therapy with APO- BISOPROLOL over approximately two weeks and the patient should be carefully

observed. The same frequency of administration should be maintained. If withdrawal symptoms occur, therapy with APO-BISOPROLOL should be reinstituted, at least temporarily.

Peripheral Vascular Disease:

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease. Caution should be exercised in such individuals.

Oculomucocutaneous Syndrome:

Various skin rashes have been reported with β-blockers, including bisoprolol. A severe syndrome (oculomucocutaneous syndrome), whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis, has occurred with the chronic use of one β- adrenoceptor blocking agent (practolol). This syndrome has not been observed with bisoprolol or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Sinus Bradycardia:

Severe sinus bradycardia, resulting from unopposed vagal activity following β-blockade, may occur with the use of APO-BISOPROLOL. In such cases, the dosage should be reduced or APO-BISOPROLOL discontinued.

Thyrotoxicosis:

In patients with thyrotoxicosis, possible deleterious effects from long-term use of APO- BISOPROLOL have not been adequately appraised.

β-adrenoceptor blockade may mask clinical signs of hyperthyroidism, such as tachycardia or its complications and gives a false impression of improvement. Abrupt withdrawal of β-blockade may be followed by an exacerbation of the symptoms of hyperthyroidism or precipitate thyroid storm.

Therefore, in such patients from whom APO-BISOPROLOL is to be discontinued, withdrawal should be gradual and the patients monitored closely.

PRECAUTIONS

Appropriate laboratory tests for monitoring renal, hepatic, and hematopoietic function should be performed at regular intervals during long-term treatment with APO-BISOPROLOL {bisoprolol fumarate).

Bronchospastic Disease:

In general, patients with bronchospastic pulmonary disease should not receive β-blockers. However, because APO-BISOPROLOL (bisoprolol fumarate) is relatively 1-selective, it may be used cautiously in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since 1-selectivity is not absolute, the lowest possible dose should be employed, a 2-agonist (bronchodilator) should be made available, and the patient should be monitored closely. In patients already on bronchodilator therapy the dose may have to be increased.

Anaesthesia:

It is not advisable to withdraw beta-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using APO-BISOPROLOL with anaesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg i.v.).

Some patients receiving beta-adrenoceptor blocking agents have been subject to protracted severe hypotension during anaesthesia. Difficulty in restarting the heart and maintaining the heart beat has also been reported (see also **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

In emergency surgery, since APO-BISOPROLOL is a competitive antagonist at beta- adrenoceptor sites, its effects may be reversed, if required, by sufficient doses of such agonists as isoproterenol or noradrenaline.

Allergic Type Reaction:

There may be increased difficulty in treating an allergic type reaction in patients on beta- blockers. In these patients, the reaction may be more severe due to pharmacologic effects of the beta-blockers and the problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm or norepinephrine to overcome hypotension.

Risk of Anaphylactic Reaction:

While taking β-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

Diabetes Mellitus and Hypoglycemia:

Beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Non-selective β-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Therefore, APO-BISOPROLOL should be used with caution in patients subject to spontaneous hypoglycemia, or in diabetic patients (especially those with labile diabetes) receiving insulin or oral hypoglycemic agents.

Impaired Renal or Hepatic Function:

Appropriate laboratory tests for monitoring renal, hepatic and hematopoietic function should be performed at regular intervals during long-term treatment. Use caution in adjusting dose in hepatic and renal impaired patients (See **DOSAGE AND ADMINISTRATION** Section).

Use in Elderly Patients:

Bisoprolol has been used in elderly patients with essential hypertension. Although the response rates and mean decreases in diastolic blood pressure were similar to that in younger patients, there was a tendency for

older patients to be maintained on higher doses of bisoprolol. Observed reductions in heart rate were slightly greater in the elderly than in the young and tended to increase with increasing dose.

Use in Pregnancy:

Bisoprolol fumarate was not teratogenic in rats at doses up to 150 mg/kg/day, which is 375 times the maximum recommended human daily dose. Bisoprolol fumarate was fetotoxic (increased late resorptions) at 50 mg/kg/day and maternotoxic (decreased food intake and body-weight gain) at 150 mg/kg/day. Bisoprolol fumarate was not teratogenic in rabbits at doses up to 12.5 mg/kg/day, which is 31 times the maximum recommended human daily dose, but was embryolethal (increased early resorptions) at 12.5 mg/kg/day.

There are no studies in pregnant women. APO-BISOPROLOL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers:

Small amounts of bisoprolol fumarate (<2% of the dose) have been detected in the milk of lactating rats. It is not known whether this drug is excreted in human milk. If use of APO- BISOPROLOL is considered essential, then mothers should stop nursing.

Pediatric Use:

Safety and effectiveness in children have not been established.

Drug Interactions:
Other β-blocking Agents: APO-BISOPROLOL should not be combined with other β-blocking agents.

Catecholamine-Depleting Drugs: Patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, should be monitored closely because the added β-adrenergic blocking action of APO-BISOPROLOL may produce excessive reduction of sympathetic activity.

Centrally Active Antihypertensive Agents: β-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the 2 drugs are co-administered, the β-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by β-blocker therapy, the introduction of β-blockers should be delayed for several days after clonidine administration has stopped (see also prescribing information for clonidine).

Antiarrhythmic Agents: APO-BISOPROLOL should be used with care when myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists [particularly of the phenylalkylamine (verapamil) and benzothiazepine (diltiazem) classes], or antiarrhythmic agents, such as disopyramide, are used concurrently.

Calcium Channel Blockers: Combined use of β-blockers and calcium channel blockers with negative inotropic effects can lead to prolongation of SA and AV conduction, particularly in patients with impaired ventricular function or conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure.

Fingolimod: Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is

not recommended. Where such coadministration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

Pharmacokinetic Interactions: Concurrent use of rifampin increases the metabolic clearance of bisoprolol, resulting in a shortened elimination half-life of bisoprolol. Therefore, compounds with enzymatic induction potential should be administered with caution to patients receiving bisoprolol therapy. Pharmacokinetic studies document no clinically relevant adverse interactions with other agents given concomitantly, including thiazide diuretics, digoxin, and cimetidine. There was no effect of bisoprolol on prothrombin time in patients on stable doses of warfarin.

Exaggerated hypertensive responses have been reported from the combined use of beta adrenergic antagonists and alpha adrenergic stimulants including those contained in proprietary cold remedies and vasoconstrictive nasal drops. Patients receiving P-blockers should be warned of this potential hazard.

INFORMATION FOR THE PATIENT

Patients, especially those with coronary artery disease, should be warned against discontinuing use of APO-BISOPROLOL (bisoprolol fumarate) without a physicians's supervision. Patients should also be advised to consult a physician if any difficulty in breathing occurs or if they develop signs or symptoms of congestive heart failure or excessive bradycardia.

Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned the β-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia, and bisoprolol fumarate should be used with caution.

ADVERSE DRUG REACTIONS

In two multi-centre, placebo-controlled clinical trials involving 404 mild-to-moderate hypertensive patients, the most frequently reported adverse reactions (>2%), whether or not drug related, were: arthralgia (2.7%), dizziness (3.5%), headache (10.9%), insomnia (2.5%), diarrhea (3.5%>), nausea (2.2%), coughing (2.5%), pharyngitis (2.2%), rhinitis (4.0%), sinusitis (2.2%), URT infection (5.0%), fatigue (8.2%), and peripheral edema (3%).

In total, 187 out of 404 patients (46.3%) reported at least one adverse event. Overall the events reported were mild to moderate in severity. Twenty-seven out of 404 patients (6.7%) discontinued therapy due to an adverse event or an intercurrent illness.

The following table (Table 1) presents the adverse experiences, whether or not drug related, reported by >1%of all patients (n=404) enrolled in the two placebo-controlled trials of bisoprolol fumarate given in single daily doses of 2.5 - 40 mg. The adverse drug reactions that appear to be dose related are bradycardia, diarrhea, asthenia, fatigue and sinusitis. As the incidence of bradycardia is 0.5%, it is the only dose related adverse experience not listed below in Table 1.

TABLE 1

Adverse Experience (>1%):

Placebo-Controlled Trials (n=404)

Body System/Adverse Experience	All Adverse Experiences n (%)
Musculo-skeletal	
athralgia	11 (2.7)
myalgia	7 (1.7)
muscle cramps	6 (1.5)
Central Nervous System	
dizziness	14 (3.5)
headache	44 (10.9)
paraethesia	5 (1.2)
hypoaesthesia	6 (1.5)
Autonomic Nervous System	
dry mouth	5 (1.2)
Hearing and Vestibular	
earache	5 (1.2)
Psychiatric	
impotence	5 (1.2)
insomnia	10 (2.5)
somnolence	5 (1.2)
Gastrointestinal	
diarrhea	14 (3.4)
dyspepsia	5 (1.2)
nausea	9 (2.2)
vomiting	6 (1.5)
Respiratory	
coughing	10 (2.5)
dyspnea	6 (1.5)
pharyngitis	9 (2.2)
rhinitis	16 (4.0)
sinusitis	9 (2.2)
URT infection	20 (5.0)
Body as Whole	
asthenia	6 (1.5)
chest pain	6 (1.5)
fatigue	33 (8.2)
edema peripheral	12 (3.0)

In one long-term, open-label, extension study involving 144 hypertensive patients, the most frequently reported adverse experiences (>2%), whether or not drug related were: arthralgia (4.2%), myalgia (2.1%), muscle cramps (2.1%), dizziness (4.9%), headache (8.3%), earache (2.1%), impotence (2.1%), libido decrease (2.1%), abdominal pain (2.1%), diarrhea (2.8%), bronchitis (2.8%), coughing (4.2%), pharyngitis (4.2%), rhinitis (8.3%), sinusitis (4.9%), URT infection (6.9%), back pain (2.1%), chest pain (2.1%), fatigue (6.9%), fever (2.1%), peripheral edema (3.5%), pain (2.1%), and traumatic injury (2.1%).

The adverse experiences reported were generally mild to moderate in severity. Seventy-nine out of 144 patients (54.9%) reported at least one adverse experience. Out of the total number of patients enrolled, 12

(8.3%) discontinued therapy due to an adverse experience or an intercurrent illness.

The table below (Table 2) presents the adverse experiences reported by at least 1%all of patients (n=144) enrolled in the long-term, open-label, extension study in which patients received doses of bisoprolol fumarate ranging from 5- 20 mg daily.

TABLE 2

Adverse Experiences (>1%): Long-Term, Open-Label, Extension Study (n=144)

Body System/Adverse Experience	**All Adverse Experiences**
Musculo-skeletal	
athralgia	6 (4.2)
myalgia	3 (2.1)
muscle cramps	3 (2.1)
Central Nervous System	
dizziness	7 (4.9)
headache	12 (8.3)
neuralgia	2 (1.4)
Vision	
eye abnormality	2 (1.4)
vision abnormality	2 (1.4)
Hearing and Vestibular	
earache	3 (2.1)
tinnitus	2 (1.4)
Psychiatric	
depression	2 (1.4)
impotence	3 (2.1)
libido decreased	3 (2.1)
insomnia	2 (1.4)
paroniria	2 (1.4)
Gastrointestinal	
abdominal pain	3 (2.1)
diarrhea	4 (2.8)
dyspepsia	2 (1.4)
Respiratory	
bronchitis	4 (2.8)
bronchospasm	2 (1.4)
coughing	6 (4.2)
pharyngitis	6 (4.2)
rhinitis	12 (8.3)
sinusitis	7 (4.9)
URT infection	10 (6.9)
Body as Whole	
allergy	2 (1.4)
back pain	3 (2.1)
chest pain	3 (2.1)
fatigue	10 (6.9)
fever	3 (2.1)
hot flushes	2 (1.4)

Body System/Adverse Experience	All Adverse Experiences
malaise	2 (1.4)
edema generalized	2 (1.4)
edema peripheral	5 (3.5)
pain	3 (2.1)
traumatic injury	3 (2.1)

The following is a list of spontaneous adverse experiences reported with bisoprolol since its entry into the U.S. market and the markets of some European countries. In these cases, an incidence or causal relationship cannot be accurately determined. The adverse experiences are listed according to body system and are as follows:

CENTRAL NERVOUS SYSTEM: Dizziness, vertigo, headache, paraesthesia, somnolence, decreased concentration/memory, aphasia, insomnia, muscle contractions (involuntary), paresis, sleep disturbances, sleepiness, syncope, tingling sensation, coma, encephalopathy, speech disorder, hallucination, confusion.

AUTONOMIC NERVOUS SYSTEM: Dry mouth.

CARDIOVASCULAR: Bradycardia, palpitations and other rhythm disturbances, hypotension, dyspnea on exertion, embolism, extrasystoles, atrial fibrillation, left cardiac failure, myocardial infarction, Raynaud-like disorder, hypertension, cardiac failure, circulatory failure, AV block, cardiac arrest, tachycardia, ventricular fibrillation, arrhythmia.

SKIN: Rash, pruritus, alopecia, angioedema, exfoliative dermatitis, hyperpigmentation, psoriaform rash, skin photosensitivity, epidermal necrolysis, erythema multiforma, scleroderma, skin discolouration, urticaria.

SPECIAL SENSES: Ocular pain/pressure, abnormal lacrimation, taste abnormalities, ageusia, anosmia, conjunctivitis, visual disturbances.

METABOLIC: Hypoglycaemia

RESPIRATORY: Asthma/bronchospasm, dyspnea, shortness of breath, pulmonary edema, pneumonitis, respiratory insufficiency.

HEMATOLOGIC: Purpura, vasculitis, peripheral ischemia.

GASTROINTESTINAL: Vomiting, diarrhea.

MUSCULOSKELETAL: Muscle cramps, twitching/tremor, arthralgia, myalgia.

GENITO-URINARY: Peyronie's disease, galactorrhea, mastalgia, still-birth.

GENERAL: Fatigue, asthenia, malaise, edema, weight gain, death, scleroderma, overdose effect, asthenia.

LABORATORY ABNORMALITIES: In clinical trials, the most frequently reported laboratory change was an increase in serum triglycerides, but this was not a consistent finding.

Sporadic liver abnormalities have been reported. In two U.S., well-controlled studies versus placebo with bisoprolol fumarate treatment for 4 - 12 weeks, the incidence of concomitant elevations in SGOT and

SGPT of between 1 -2 times normal was 3.9%, for bisoprolol fumarate compared to 2.5% for placebo. No patient had concomitant elevations greater than twice normal.

Experience from long-term, uncontrolled studies with bisoprolol fumarate treatment for 6 - 18 months, the incidence of one or more concomitant elevations in SGOT and SGPT of between 1- 2 times normal was 6.2%. The incidence of multiple occurrences was 1.9%. For concomitant elevations in SGOT and SGPT of greater than twice normal, the incidence was 1.5%. The incidence of multiple occurrences was 0.3%. In many cases these elevations were attributed to underlying disorders, or resolved during continued treatment with bisoprolol fumarate.

Other laboratory changes include small increases in uric acid, creatinine, BUN, serum potassium, glucose, and phosphorus and decreased in WBC and platelets. These were generally not of clinical importance and rarely resulted in discontinuation of bisoprolol fumarate.

As with other beta-blockers, ANA conversions have also been reported on bisoprolol fumarate. About 15% of patients in long-term studies converted to a positive titre, although about one- third of these patients subsequently reconverted to a negative titre while on continued therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The most common signs expected with overdosage of a Ββ-blocker are bradycardia, hypotension, congestive heart failure, bronchospasm, and hypoglycemia. To date, a few cases of overdose with APO-BISOPROLOL (bisoprolol fumarate) have been reported. Bradycardia and/or hypotension were noted. Sympathomimetic agents were given in some cases, and all patients recovered. In general, if overdose occurs, therapy with APO-BISOPROLOL should be stopped and supportive, symptomatic treatment should be provided. Patients should be monitored closely. Limited data suggest that bisoprolol is not dialysable.

Based on the expected pharmacologic actions and recommendations for other β-blockers, the following general measures should be considered when clinically warranted:

Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary. Intravenous glucagon has been described to be useful.

Hypotension: IV fluids and vasopressors such as dopamine or norepinephrine should be administered. Monitor blood pressure continuously. Intravenous glucagon may be useful.

Heart Block (second or third degree): Patients should be carefully monitored and treated with isoproterenol infusion or transvenous cardiac pacemaker insertion, as appropriate.

Congestive Heart Failure: Initiate conventional therapy (i.e., digitalis, diuretics, inotropic agents, vasodilating agents). Glucagon has been reported to be useful.

Bronchospasm: Administer bronchodilator therapy such as isoproterenol or terbutaline (P2 stimulants) and/or IV aminophylline.

Hypoglycemia: Administer IV glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for

administering cardiac and respiratory support.

It should be remembered that APO-BISOPROLOL is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of APO-BISOPROLOL. However, complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

In the treatment of mild to moderate hypertension APO-BISOPROLOL (bisoprolol fumarate) must be individualized to the needs of the patient. The usual starting dose is 5 mg once-daily either added to a diuretic or alone. If the response to 5 mg is inadequate, the dose may be increased to 10 mg and then, if necessary, to 20 mg once daily. An appropriate interval for dose titration is 2 weeks.

Increasing the dose beyond 20 mg once daily produces only a small incremental benefit.

Patients with Renal or Hepatic Impairment:

In patients with hepatic impairment (hepatitis or cirrhosis) or renal dysfunction (creatinine clearance less than 40 ml/min) as in other patients, the initial daily dose should be 5 mg. Because of the possibility of accumulation, caution must be used in dose-titration. Since limited data suggest that APO-BISOPROLOL is not dialysable, drug replacement is not necessary in patients undergoing dialysis.

Elderly: In the elderly, it is not usually necessary to adjust the dose, unless there is also significant renal or hepatic dysfunction (see **PRECAUTIONS**).

Children:
There is no pediatric experience with APO-BISOPROLOL, therefore its use cannot be recommended for children.

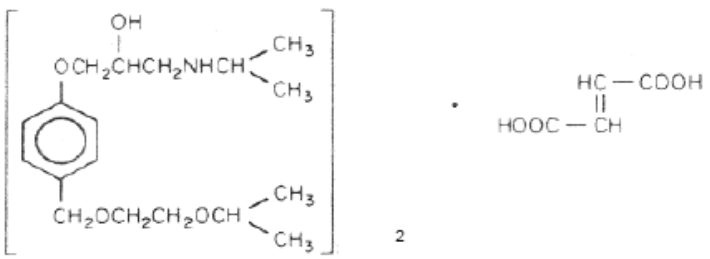
PHARMACEUTICALINFORMATION

DRUG SUBSTANCE:

Proper name: Bisoprolol fumarate

Chemical name: (+/-) -1- [4- [[2- (1-Methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl) amino] -2-propanol *(E)* -2-butenedioate (2:1) (salt)

Structural Formula:



Molecular weight: 766.97

Physical form: White crystalline powder

Solubilities:

Solvent	Solubility (g/ml)
Methanol	1
Water	0.6
Ethanol	0.5
Chloroform	0.5
Acetone	0.009
Ethylacetate	0.0016

pH Values: pH of a 5% Solution: 6 - 7

Dissociation Constants:

The pKa value for bisoprolol free base is 9.5 by potentiometric titration. The pKa values for fumaric acid are 3.03 and 4.44.

Partial co-efficients:

pH PARTITION COEFFICIENT IN OCTANOL/BUFFER SYSTEM:

BUFFER pH	APPARENT PARTITION COEFFICIENT
2.0	0.24
3.0	0.20
4.0	0.16
5.0	0.13
6.0	0.24
7.0	1.09
8.0	7.9
9.0	5.6

Melting Point: 100 - 103°C by the capillary method.

Specific Rotation: Bisoprolol fumarate is a racemic mixture of S(-) and R(+) enantiomers. In assay of bulk material, the specific rotation was zero, within the error of measurement.

Composition:
In addition to the active ingredient bisoprolol fumarate, each tablet contains the non-medicinal ingredients lactose monohydrate, microcrystalline cellulose, magnesium stearate, crospovidone, hyroxypropyl

methylcellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide.

The 5 mg tablets also contain red ferric oxide.

STABILITY AND STORAGE RECOMMENDATIONS

APO-BISOPROLOL (bisoprolol fumarate) tablets should be stored at controlled room temperature 15°C-30°C. No other special storage conditions are necessary.

AVAILABILITY OF DOSAGE FORMS

APO-BISOPROLOL Tablets 5 mg:

Salmon pink, round, biconvex, film-coated tablets. Scored and engraved "BI" over "5" on one side and "APO" on the other. Available in bottles of 100.

APO-BISOPROLOL Tablets 10 mg:

White, round, biconvex, film-coated tablets. Engraved "BI" over "10" on one side and "APO" on the other. Available in bottles of 100.

PHARMACOLOGY

HUMAN PHARMACOLOGY

β_1-selectivity of bisoprolol fumarate has been demonstrated in both animal and human studies. No effects at therapeutic doses on β_2-adrenoceptor density have been observed. Pulmonary function studies have been conducted in volunteers, asthmatics, and patients with chronic obstructive pulmonary disease (COPD) utilizing pulmonary function testing. Bisoprolol fumarate doses ranged from 5 to 60 mg, atenolol from 50 to 200 mg, metoprolol from 100 to 200 mg, and propranolol from 40 to 80 mg. In some studies, slight, asymptomatic increases in airway resistance (AWR) and decreases in forced expiratory volume (FEV_1) were observed with doses of bisoprolol fumarate 20 mg and higher, similar to the small increased in AWR also noted with the other cardioselective β-blockers. The changes induced by β-blockade with all agents were reversed by bronchodilator therapy.

TOXICOLOGY

Toxicology studies in animals have established that bisoprolol fumarate has a wide margin of safety.

In multiple-dose studies in the rat and dog, findings were related to pharmacologic effects and/or were class effects known to occur with other β-blockers and thus were not specific to bisoprolol fumarate. In the rat, at high multiples of human therapeutic doses, increased serum triglycerides, focal myocardial necrosis, increased heart weight/size, and pulmonary phospholipidosis were observed. In the dog, the tolerance threshold for bisoprolol fumarate was determined by its pharmacologic actions (i.e., hypotension) which resulted in lethality. Increases in serum triglycerides and hepatocyte inclusion bodies were also seen in dogs.

Acute Toxicity:

The acute toxicity of bisoprolol fumarate was studied in mice, rats, and dogs. Tables 3A and 3B below summarize the results of the studies performed:

TABLE 3A: ACUTE TOXICITY: BISOPROLOL ALONE

Species/Strain	No./Sex/Dose	Route	LD 50 (mg/kg)
Mice: EMD: NMRI (SPF)	50M 50F	PO	730
Mice: EMD: NMRI (SPF)	35M 35F	IV	130
Rat: EMD Wistar-AF/ (SPF)	45M 45F	PO	1112
Rat: EMD Wistar-AF/ (SPF)	35M 35F	IV	50

Dog: BMD: Beagle	24M 24F	PO	90
Dog: BMD: Beagle	20M 20F	IV	24

TABLE 3B: ACUTE TOXICITY BISOPROLOL/HCTZ (1:2.5 COMBINATION)

Species/Strain	**No./Sex/Dose**	**Route**	**LD 50 (BIS+HCTZ) (mg/kg)**
Mouse: EMD: NMRI (SPF)	150M 150F	PO Gavage	1050+2620
Rat: EMD Wistar-AF/ (SPF)	15M 15F	PO Gavage	950+2370

Clinical signs in mice and rats were reduced spontaneous activity, prone position, and dyspnea. In mice, convulsions and tremor were also observed. Dogs were more sensitive to bisoprolol fumarate than rodents. Clinical signs in dogs were staggering, salivation, vomiting, prone or lateral position, dyspnea, convulsions, and tonic spasms. In all three species, clinical signs were seen soon after dosing and subsided rapidly in animals that survived. Delayed effects were not observed.

LD50's of the S(-)-enantiomer in mice and rats were similar to or greater than LD50's for bisoprolol fumarate (racemate).

Clinical signs in mice and rats were reduced spontaneous activity, twitching, prone position, trembling, dyspnea, and piloerection. In both species, clinical signs were seen soon after dosing. Clinical signs subsided rapidly in mice that survived, but were seen up to day 6 in rats that survived. There was no potentiation of the acute toxicity of bisoprolol fumarate when it was given in combination with hydrochlorothiazide to mice or rats.

Multiple-Dose Toxicity:

The toxicity of bisoprolol fumarate was studied using daily oral doses in rats for 6 weeks, and 3, 6, and 12 months, and in dogs for 1, 6, and 12 months.

A 1-month daily IV dosing study was conducted in rats and dogs. The toxicity of bisoprolol fumarate in combination with hydrochlorothiazide was studied in each species using daily oral dosing for 6 months.

The results of the studies performed are displayed in tables 4A and 48 below:

Myocardial Necrosis:

A listing of the myocardial necrosis studies performed can be found in tables 5A and 58. Minimal focal myocardial necrosis and/or fibrosis, accompanied by varying amounts of inflammatory infiltrates were seen in

myocardial sections of both control and treated male (but not female) animals in the 6-month study of bisoprolol fumarate in combination with hydrochlorothiazide. In general, the focal myocardial changes in control and treated rats did not differ in morphology, severity, or location in the myocardium. Group incidence rates appeared to be higher in the active treatment groups than in the controls.

Cardioactive drugs, as a pharmacologic class, are known to produce myocardial changes in rats (Van Vleet and Ferrans, 1986) and minimal focal myocardial necrosis and/or fibrosis is commonly seen in untreated male rats (Boorman, 1981; Greaves and Faccini, 1984). Results of the two 3-month rat studies indicated the following: (1) High multiples of human therapeutic doses of bisoprolol fumarate, metoprolol, and hydrochlorothiazide alone and in combination increased the group incidence of focal myocardial necrosis/fibrosis in male rats. (2) When bisoprolol fumarate was given in combination with hydrochlorothiazide, the group incidence of focal myocardial necrosis/fibrosis appeared slightly higher than when each agent was given alone. (3) Myocardial changes described have the same morphology and severity in control and drug-treated groups.

TABLE 4A: SUBACUTE AND CHRONIC TOXICITY: BISOPROLOL ALONE

Species/ Strain	**No./ Sex** *I*	**Route**	**Dose Group (mg/kg/day)**	**Duration (weeks)**	**Results**
Rat: Wistar-AF HAN/SPF	10	PO-Gavage	0, 20, 60, 180, 540	6	– Dose dependent increase in serum triglycerides at 60-540 mg/kg/day – Increased incidence of pulmonary phospholipidosis at 180 mg/kg/day. Changes were reversible following cessation of treatment – Adrenal cortical nodules observed in all of F
Rat: Wistar-AF HAN/SPF	10	PO-Diet	0, 100, 150, 225, 350, 500	13	– Increased heart weight, circumference and volume. Increased left ventricular volume and surface[a] – Increased incidence of phospholipidosis 225 mg/kg/day – Adrenal cortical nodules observed in all treated F
Rat: Wistar-AF HAN/SPF	25	PO-Gavage	0, 15, 50, 150	26 (with 4 wk recovery)	– Dose dependent increase in serum triglycerides at 50 - 150 mg/kg/day – Increased heart weight, volume and circumference. Increase in left ventricular volume and surface[a] – Adrenal cortical nodules observed in all F
Rat: Wistar-AF HAN/SPF	20	PO-Diet	0, 25, 75, 225	52 (with 13 wk recovery)	– Increased heart weight, volume and circumference. - Increase in left ventricular volume and surface[a]
Rat: Wistar-AF HAN/SPF	12	IV	0, 0.2, 1, 5	4 (with 4 wk recovery)	– No drug related deaths or antemortem or post mortem findings

Species/ Strain	No./ Sex *I*	Route	Dose Group (mg/kg/day)	Duration (weeks)	Results
Dog: Beagle	3	PO-Capsule	0, 3, 10, 30, 100	4	- Tremors, lethargy and transient bradycardia at100 mg/kg/day - 1 death at 100 mg/kg/day b - Salivation and vomiting up to 3 hrs post dosing at 100 mg/kg/day
Dog: Beagle	8 6 6 8	PO-Capsule	0 10 27 73	26 (with 8 wks recovery)	- *J* 2 deaths at 73 mg/kg/day - Salivation, vomiting, tremor, staggering and lethargy at -c.27 mg/kg/day - Slight reduction in mean systolic BP and HR in all test groups - Hepatocyte inclusion bodies at -c.27
Dog: Beagle	6	PO-Capsule	0, 3, 10, 30	52 (with 8 wks recove ry)	- 1 death at 30 mg/kg/day b - Salivation and emesis up to 3 hours after closing at 30 mg/kg/day - Mean HR increase at all doses - Hepatocyte inclusion bodies in control and test groups
Dog: Beagle	2	IV	0, 1, 3, 10	4	- No death or toxicity
Dog: Beagle	5 or 8	PO-Capsules	0, 3, 10, 30	52	- 10 deaths at 30 mg/kg, 1 death at 10 mg/kg - Salivation emesis, lacrimation, soft stool at all test doses - Serum triglycerides increase in at all test doses
Dog: Beagle	5 or 8	PO-Capsules	20, 30	52	- 4 deaths at 20 mg/kg/day - Prolonged PR interval, primary AV block and atrial and ventricular premature complexes in all surviving animals - Salivation, emesis, lacrimation, soft stool in both test groups - Increased serum triglycerides

TABLE 4B: SUBACUTE AND CHRONIC TOXICITY: BISOPROLOL AND HCTZ IN A 1:25 RATIO

Species/Strain	No./Sex/ Dose	Route	Dose Group BIS+HCTZ (mg/kg/	Duration (Weeks)	Results
Rat: Wistar-AFHAN/SPF	1510	PO-Garage	0 10.5 (3+7.5) 35 (10+25) 105 (30+75) 7.5 (HCTZ alone) 75 (HCTZ	26 (with 8 wks recovery)	- HR decreased at 10:25 mg/kg/day - Burrowing and salivation at 10:25 and 30:75 mg/kg/day - Minimal focal myocardial necrosisa and/or fibrosis, with varying amounts of inflammatory infiltrates in control and treated males - Group incidence rates for focal myocardial changes appear to be higher in animals given bisoprolol alone, HCTZ alone or the combination then in the controls
Dog: Beagle	5	PO-Capsule	0 10.5 (3+7.5) 35 (10+25) 25 (HCTZ alone)	26 (with 8 wks recovery)	- Slight decrease in the HR and slight prolongation of PQ interval at 3:7.5 and 10:25 mg/kg/day - Sporadic changes in organ weight - Increase in single cell hepatocellular necrosis seen at 10:25 mg/kg/day and HCTZ groups - Increase in binucleated hepatocytes in the 10:25 mg/kg/day group - Single cell hepatocellular necrosis was the only histopathological change seen after recovery

(a) regarding myocardial necrosis please see Table 5A and 58
(b) cardiovascular collapse due to impulse formation and conduction disturbances

TABLE 5A

Myocardial Necrosis in Studies with Bisoprolol and Bisoprolol/Hydrochlorothiazide (1:2.5) Combination in Male Rats

Study	Summary Incidence of Myocardial Necrosis			
Dose (mg/kg):	0	15	50	150
3 Months Bisoprolol	1/5	1/5	2/5	*215*
6 Months Bisoprolol	6/10	3/10	5/10	7/10
6 Months Bisoprolol with 2 Months Recovery	3/10	3/10	0/10	3/10

Study	Summary Incidence of Myocardial Necrosis					
Dose (mg/kg) : Bisoprolol Hydrochlorothiazide	0 0	3 7.5	10 25	30 75	0 7.5	0 75
6 Months Bisoprolol	1/10	5/10	6/10	7/10	2/5	215
6 Months Bisoprolol with 2 Months Recovery	1/5	-	-	2/5	-	215

Study	Summary Incidence of Myocardial Necrosis			
Dose (mg/kg) :	0	25	75	225
12 Months Bisoprolol	5/10	8/10	5/10	7/10
12 Months Bisoprolol with 3 Months Recovery	5/10	4/10	4/10	5/10

TABLE 5B

Myocardial Necrosis in 3-Month Studies with Bisoprolol Metoprolol and Hydrochlorothiazide in Male Rats

Summary Incidence of Myocardial Necrosis				
Group:	**Control**	**Bisoprolol**	**Hydrochlorothiazide**	**Bisoprolol + Hydrochlorothiazide**
Dose (mg/kg):	0	30	75	30 +75
Incidence	5/20	8/20	6/20	12/10
Group:	**Control**	**Metoprolol**	**Hydrochlorothiazide**	**Metoprolol + Hydrochlorothiazide**
Dose (mg/kg):	0	300	150	300 + 150
Incidence	2/20	16/20	9/20	14/20

In conclusion, bisoprolol fumarate and metoprolol, alone or in combination with hydrochlorothiazide, and hydrochlorothiazide alone are associated with an increased incidence of minimal myocardial changes in male rats given high multiples of human therapeutic doses. These myocardial changes are not severe and the effect is species-and sex-specific. The myocardial changes discussed above are most likely a class effect, probably due to the exaggerated pharmacologic actions of these drugs at high doses. Metoprolol has been marketed and used clinically for more than 10 years, hydrochlorothiazide for more than 20 years, and fixed combinations of metoprolol and hydrochlorothiazide for several years. Therefore, the myocardial findings in these studies are not considered to indicate any potential risk for man.

Carcinogenicity:

Long-term studies were conducted with oral bisoprolol fumarate administered in the feed of mice (20 and 24 months) and rats (26 months). No evidence of carcinogenic potential was seen in mice dosed up to 250 mg/kg/day or rats dosed up to 123 mg/kg/day. On a body-weight basis, these doses are 625 and 312 times, respectively, the maximum recommended human dose (MRHD) of 20 mg, (or 0.4 mg/kg/day based on a 50 kg individual); on a body-surface-area- basis, these doses are 59 times (mice) and 64 times (rats) the MRHD.

Teratology and Reproduction:

In reproductive toxicology studies in rats, bisoprolol fumarate had no effect on fertility or general reproductive performance. Bisoprolol fumarate, like other β-blockers, caused maternal and embryo toxic effects at high doses, but was not teratogenic in either rats or rabbits. In a perinatal and postnatal study in rats, maternal toxic effects and reduced birth weight were observed at the high dose, but no other effects on reproductive performance were seen.

Bisoprolol fumarate was fetotoxic (increased late resorptions) at 50 mg/kg/day and maternotoxic (decreased food intake and body weight gain) at 150 mg/kg/day. The fetotoxicity in rats occurred at 125 times the MRHD on a body-weight-basis and 26 times the MRHD on the basis of body-surface area. The maternotoxicity occurred at 375 times the MRHD on a body- weight basis and 77 times the MRHD on the basis of body-surface area. In rabbits, bisoprolol fumarate was not teratogenic at doses up to 12.5 mg/kg/day, which is 31 and 12 times the MRHD based on body-weight and body-surface-area, respectively, but was embryolethal (increased early resorptions) at 12.5 mg/kg/day.

Mutagenicity:

The mutagenic potential of bisoprolol fumarate was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosome aberration assays in Chinese hamster V79 cells, the unscheduled DNA synthesis test, the micronucleus test in mice, and cytogenetics assay in rats. There was no evidence of mutagenic potential in these in vitro and in vivo assays.