Product Monograph

Sandoz Bisoprolol

Bisoprolol fumarate tablets, USP

5 mg, 10 mg

β-adrenoceptor blocking agent

Sandoz Canada Inc.
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5 mg, 10 mg

Pharmacological Classification

β-adrenoceptor blocking agent

ACTION AND CLINICAL PHARMACOLOGY

Sandoz Bisoprolol (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 dose bisoprolol may also inhibit β_2-adrenoceptors, located chiefly in the bronchial and vascular musculature.

Pharmacodynamics
The most prominent effect of bisoprolol fumarate 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.

Mechanism of Action
The mechanism of action of its antihypertensive effects has not been completely established. Factors which may be involved include:
- Antagonism of β-adrenoceptors to decreased cardiac output.
- Inhibition of renin release by the kidneys.
- Diminution of tonic sympathetic outflow from the vasomotor centers in the brain.

In normal volunteers, bisoprolol fumarate therapy resulted in a reduction of exercise and isoproterenol-induced 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 fumarate 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 at 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 2 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 fæces. 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.

A comparative, randomized, single-dose, 2-way crossover bioavailability study of Sandoz Bisoprolol 10 mg tablets was performed *vs* the Canadian reference in healthy adult males under fasting conditions.The summary of the comparative bioavailability study carried out by Sandoz Canada Inc. is presented in the following table:

Summary Table of the Comparative Bioavailability Data
(1x10 mg) Sandoz Bisoprolol
From measured data

PARAMETER	Geometric Mean Arithmetic Mean (CV%)		%RATIO OF GEOMETRIC MEANS
	TEST	REFERENCE*	
AUC_{0-T} (ng.hr/mL)	609.80 615.79 (14.33)	618.42 625.50 (15.17)	98.61
AUC_I (ng.hr/mL)	642.87 650.16 (15.29)	652.76 661.07 (15.95)	98.48
C_{max} (ng/mL)	40.37 40.78 (15.27)	38.20 39.20 (16.48)	104.32
T_{max} (h)**	2.80 (44.26)	3.47 (46.71)	
$T_{½}$ (h)**	11.07 (13.40)	11.13 (13.47)	

* Monocor®, Crystaal a Division of Biovail Corporation, Canada.
** The T_{max} and $T_{½}$ parameters are to be expressed as the arithmetic means (CV%).

INDICATIONS AND CLINICAL USE

Sandoz 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.

Sandoz Bisoprolol is not recommended for the emergency treatment of hypertensive crisis.

CONTRAINDICATIONS

Sandoz 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 bisoprolol fumarate to patients with a history of severe heart failure. Safety and effectiveness of bisoprolol doses higher than 10 mg/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 heart 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. Bisoprolol fumarate acts selectively without abolishing the effects of digitalis. However, the positive inotropic effect of digitalis may be reduced by the negative inotropic effect of bisoprolol fumarate 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, bisoprolol fumarate therapy should be immediately withdrawn.

Abrupt Cessation of Therapy with 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 bisoprolol fumarate 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 bisoprolol fumarate 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 fumarate. 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 fumarate 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 bisoprolol fumarate. In such cases, the dosage should be reduced or bisoprolol fumarate discontinued.

Thyrotoxicosis
In patients with thyrotoxicosis, possible deleterious effects from long-term use of bisoprolol fumarate 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 patient from whom bisoprolol fumarate is to be discontinued, withdrawal should be gradual and the patient monitored closely.

PRECAUTIONS

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

Bronchospastic Disease
In general, patients with bronchospastic pulmonary disease should not receive β-blockers. However, because bisoprolol fumarate is relative β_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 β_1-selectivity is not absolute, the lowest possible dose should be employed, a β_2-agonist (bronchodilator) should be made available, and the patient should be monitored closely. In patients already on bronchodilators therapy, the dose may have to be increased.

Anæsthesia
It is not advisable to withdraw β-adrenoceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using bisoprolol fumarate with anæsthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1 to 2 mg IV).

Some patients receiving beta-adrenoceptor blocking agents have been subject to protracted severe hypotension during anæsthesia. 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 bisoprolol fumarate 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 a beta-agonist 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 beta-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Therefore, bisoprolol fumarate 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**).

Geriatrics
Bisoprolol fumarate 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 fumarate. Observed reductions in heart rate were slightly greater in the elderly than in the young and tended to increase with increasing dose.

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. Bisoprolol fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
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 bisoprolol fumarate is considered essential, then mothers should stop nursing.

Children
Safety and effectiveness in children have not been established.

Drug Interactions

Other β-blocking Agents:
Bisoprolol fumarate 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 bisoprolol fumarate 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 two drugs are coadministered, 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
Bisoprolol fumarate should be used with care when myocardial depressants or inhibitors of A-V 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 S-A and A-V conduction, particularly in patients with impaired ventricular function or conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure.

Pharmacokinetic Interactions
Concurrent use of rifampin increases the metabolic clearance of bisoprolol fumarate, resulting in a shortened elimination half-life of bisoprolol fumarate. Therefore, compounds with enzymatic induction potential should be administered with caution to patients receiving bisoprolol fumarate 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 fumarate on prothrombin time in patients on stable doses of warfarin.

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

Information to the Patient
Patients, especially those with coronary artery disease should be warned against discontinuing use of bisoprolol fumarate without a physicians 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 that 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. (Table 1).

Table 1-Adverse Experience (>1%): Placebo-Controlled Trials (n=404)

Body System/Adverse Experience	All Adverse Experiences n (%)
Musculoskeletal	
Arthralgia	11 (2.7)
Myalgia	7 (1.7)
Muscle cramps	6 (1.5)
CNS	
Dizziness	14 (3.5)
Headache	44 (10.9)
Paresthesia	5 (1.2)
Hypoesthesia	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 a 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% of all patients (n=144) enrolled in the long-term, open-label, extension study in which patients received doses of bisoprolol fumarate ranging from 5 to 20 mg daily.

Table 2-Adverse Experience (>1%): Long-Term, Open-label, Extension Study (n=144)

Body System/Adverse Experience	All Adverse Experiences n (%)
Musculoskeletal	
Arthralgia	6 (4.2)
Myalgia	3 (2.1)
Muscle cramps	3 (2.1)
CNS	
Dizziness	7 (4.9)
Headache	12 (8.3)
Neuralgia	2 (1.4)
Vision	
Eye abnormality	2 (1.4)
Vision abnormal	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 a 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)
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 experience reported with bisoprolol fumarate since its entry into the US market and the markets of some European countries. In these cases, an incidence of causal relationship cannot be accurately determined. The adverse experiences are listed according to body system and are as follows:

CNS (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, A-V block, cardiac arrest, tachycardia, ventricular fibrillation, arrhythmia.

Skin
Rash, pruritus, alopecia, angioedema, exfoliative dermatitis, hyperpigmentation, psoriaform rash, skin photosensitivity, epidermal necrolysis, erythema multiforme, scleroderma, skin discolouration, urticaria.

Special Senses
Ocular pain/pressure, abnormal lacrimation, taste abnormalities, ageusia, anosmia, conjunctivitis, visual disturbances.

Metabolic
Hypoglycemia.

Respiratory
Asthma/bronchopasm, dyspnea, shortness of breath, pulmonary edema, pneumonitis, respiratory insufficiency.

Hematologic
Purpura vasculitis and peripheral ischemia.

Gastrointestinal
Vomiting and diarrhea.

Musculoskeletal
Muscle cramps, twitching/tremor, arthralgia and myalgia.

Genitourinary
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 to 18 months, the incidence of one or more concomitant elevations in SGOT and SGPT of between 1 to 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 β-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 β-blockers are bradycardia, hypotension, congestive heart failure, bronchospasm and hypoglycemia. To date, a few cases of overdose with 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 bisoprolol fumarate should be stopped and supportive, symptomatic treatment should be provided. Patients should be monitored closely. Limited data suggest that bisoprolol fumarate 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 (β_2 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 bisoprolol fumarate 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 bisoprolol fumarate. However, complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

In the treatment of mild to moderate hypertension, Sandoz 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 bisoprolol fumarate is not dialysable, drug replacement is not necessary in patients undergoing dialysis.

Geriatrics
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 bisoprolol fumarate, therefore, its use cannot be recommended for children.

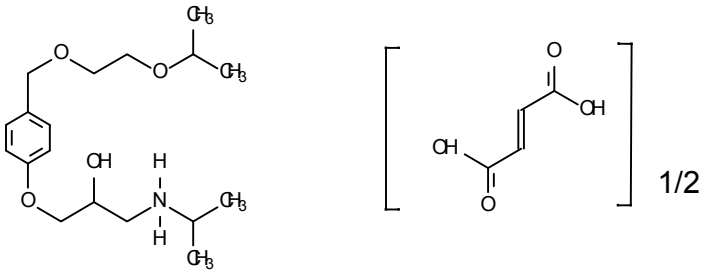
PHARMACEUTICAL INFORMATION

Drug Substance

Common 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 formula: $(C_{18} H_{31} NO_4)_2 . C_4H_4O_4$

Molecular weight: 766.96

Description: White crystalline powder

pH values: pH of a 1% solution: 6.0 and 7.0

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

Melting point: 100 - 103ºC 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.

Partition coefficient: 0.129

Solubilities: Bisoprolol Hemifumarate is soluble in Water and Methanol.

STABILITY AND STORAGE RECOMMENDATIONS

Sandoz Bisoprolol (bisoprolol fumarate) tablets should be stored between 15 and 30ºC. No other special storage conditions are necessary.

AVAILABILITY OF DOSAGE FORMS

5 mg Tablet: Each pink film-coated round, biconvex tablets imprinted “E” over “771" on one side and bisected on the other side contain 5 mg of bisoprolol fumarate. Available in white plastic bottles of 30 and 100 tablets.

Nonmedicinal ingredients: Microcrystalline cellulose, dibasic calcium phosphate anhydrous, cornstarch, colloidal silicon dioxide, magnesium stearate, FD&C yellow #6 aluminum lake, FD&C red #40 aluminum lake, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

10 mg Tablet: Each white film-coated round, biconvex tablets imprinted “E” over “774" on one side and bisected on the other side contain 10 mg of bisoprolol fumarate. Available in white plastic bottles of 30 and 100 tablets.

Nonmedicinal ingredients: Microcrystalline cellulose, dibasic calcium phosphate anhydrous, cornstarch, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

INFORMATION FOR THE PATIENT

The following contains important information you should know about Sandoz Bisoprolol (bisoprolol fumarate) tablets. Sandoz Bisoprolol is for once-daily use. It belongs to the group of drugs called "beta-blockers". Your doctor may have prescribed Sandoz Bisoprolol to help control hypertension (high blood pressure). Sandoz Bisoprolol decreases blood pressure and reduces how hard the heart has to work.

Read the following carefully. It does not replace your doctor's or pharmacist's advice. They may have given you different instructions for your particular health condition. Be sure to follow their advice. If you have any questions, talk to your doctor or pharmacist.

Before you take Sandoz Bisoprolol you should tell your doctor the following:

- If you are pregnant or plan to become pregnant.
- If you are breastfeeding.
- About all health problems you have or have had in the past, including: asthma, bronchitis, emphysema, or other lung diseases; heart, kidney or liver disease; diabetes or an overactive thyroid gland.

- If you visit more than one doctor, make sure each knows about all the medicines you are taking, including ones you can buy without a prescription, especially diuretics (water pills), cold remedies, nasal decongestants and other heart or blood pressure medication.
- Before having surgery, tell your doctor or dentist that you are taking Sandoz Bisoprolol.
- If you are allergic to nonmedicinal substances like food products, preservatives or dyes, which may be present in Sandoz Bisoprolol tablets (see **Sandoz Bisoprolol Ingredients**).
- If you have ever had a bad, or unusual or allergic reaction to any drug containing bisoprolol in the past.

Sandoz Bisoprolol Ingredients: Bisoprolol fumarate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, cornstarch, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. The 5 mg tablets also contain FD&C yellow #6 aluminum lake and FD&C red #40 aluminum lake.

How to take Sandoz Bisoprolol: Take Sandoz Bisoprolol **exactly** as your doctor tells you. Do not miss doses or take extra doses, unless your doctor tells you. If you are not clear about the directions, ask your doctor or pharmacist.

- Sandoz Bisoprolol is taken once daily.
- Sandoz Bisoprolol may have been prescribed along with other medications to help control your particular health condition; it is important that you take these medications as prescribed.
- It is important to take Sandoz Bisoprolol at about the same time every day.
- If you miss a dose, check with your doctor or pharmacist to see what you should do.
- Tablets are not to be chewed or crushed.

Side Effects: Sandoz Bisoprolol, like any medication, may have some side effects. It is important that you keep your doctor informed of all side effects especially if you experience one of the following for several days. The most common side effects, whether or not caused by Sandoz Bisoprolol, are: headache, fatigue, urinary tract infection, rhinitis or sinusitis (inflammation in the nose), diarrhea, dizziness, peripheral edema (swelling of the ankles), joint pain, cough, insomnia (trouble sleeping), nausea (feeling like vomiting), and sore throat. You must seek medical attention immediately if you experience an allergic reaction with symptoms of rash, itching, swelling, dizziness or trouble-breathing.

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. Discuss how you feel on Sandoz Bisoprolol with your doctor or pharmacist. **Do not stop or restart Sandoz Bisoprolol on your own.**

Some precautions you should take:

- Keep Sandoz Bisoprolol out of sight and reach of children.
- Do not give Sandoz Bisoprolol to other patients because it may not be suitable for them.
- Read your prescription label carefully. Consult your doctor or pharmacist if you have any questions.

Storage: This drug should be stored between 15 and 30ºC.

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 increase 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 Fumarate Alone

Species/Strain	No./Sex/Dose	Route	LD50 (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 Fumarate/HCTZ (1:2.5 Combination)

Species/Strain	No./Sex/Dose	Route	LD50 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.

LD_{50}'s of the S (-)-enantiomer in mice and rats were similar to or greater than LD_{50}'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 in 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 table 4A and 4B below.

Myocardial Necrosis
A listing of the myocardial necrosis studies performed can be found in tables 5A and 5B. 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 Fumarate Alone

Species/Strain	No./Sex/ Dose	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 - Gavage	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 of F.
Rat: Wistar-AF HAN/SPF	25	PO - Gavage	0, 15, 50, 150	26 with 4 week 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 of F.

Table 4A: Subacute and Chronic Toxicity: Bisoprolol Fumarate Alone (continued)

Species/Strain	No./Sex/ Dose	Route	Dose Group (mg/kg/day)	Duration (weeks)	Results
Rat: Wistar-AF HAN/SPF	20	PO - Diet	0, 25, 75, 225	52 (with 13 week 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 week recovery)	-No drug related deaths or antemortem or postmortem findings.
Dog: Beagle	3	PO- Capsule	0, 3, 10, 30, 100	4	-Tremors, lethargy and transient bradycardia at 100 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 weeks recovery)	-12 Deaths at 73 mg/kg/day[b]. -Salivation, vomiting, tremor, staggering and lethargy at ≥27 mg/kg/day. -Slight reduction in mean systolic BP and HR in all test groups. -Hepatocyte inclusion bodies at ≥27 mg/kg/day.
Dog: Beagle	6	PO- Capsule	0, 3, 10, 30	52 (with 8 weeks recovery)	-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 Fumarate and HCTZ in a 1:25 Ratio

Species/Strain	No./Sex/ Dose	Route	Dose Group BIS+HCTZ (mg/kg/day)	Duration (weeks)	Results
Rat: Wistar-AF HAN/SPF	1510	PO - Gavage	0 10.5 (3+7.5) 35 (10+25) 105 (30+75) 7.5 (HCTZ alone) 75 (HCTZ alone)	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 necrosis[a] 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 fumarate alone, HCTZ alone or the combination than 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 5B
(b) cardiovascular collapse due to impulse formation and conduction disturbances

Table 5A
Myocardial Necrosis in Studies with Bisoprolol Fumarate and Bisoprolol/Hydrochloride (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	2/5
6 Months Bisoprolol	6/10	3/10	5/10	7/10
6 Month 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	2/5
6 Month Bisoprolol with 2 Months Recovery	1/5	-	-	2/5	-	2/5

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 Month Bisoprolol with 3 Months Recovery	5/10	4/10	4/10	5/10

Table 5B

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

Summary Incidence of Myocardial Necrosis				
Group	**Control**	**Bisoprolol Fumarate**	**Hydrochlorothiazide**	**Bisoprolol Fumarate+ 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 embryotoxic 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.

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