

PRODUCT MONOGRAPH

<sup>Pr</sup>TEVA-BISOPROLOL

5 mg, 10 mg Bisoprolol Fumarate Tablets

USP

$\beta$ -adrenoceptor blocking agent

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PrTEVA-BISOPROLOL

(bisoprolol fumarate)

Tablets, 5 and 10 mg

USP

**PHARMACOLOGICAL CLASSIFICATION** $\beta$ -adrenoceptor blocking agent**ACTION AND CLINICAL PHARMACOLOGY**

TEVA-BISOPROLOL (bisoprolol fumarate) is a synthetic  $\beta_1$ -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  $\beta_2$ -adrenoceptors, located chiefly in the bronchial and vascular musculature.

**Pharmacodynamics**

The most prominent effect of TEVA-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  $\beta$ -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 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 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.

A comparative, two-way, single-dose bioavailability study was performed under fasting conditions on TEVA-BISOPROLOL (bisoprolol fumarate) 10 mg tablets and MONOCOR<sup>®</sup> 10 mg tablets. The pharmacokinetic data calculated for the two bisoprolol formulations are tabulated below:

TABLE OF COMPARATIVE BIOAVAILABILITY DATA  
TEVA-BISOPROLOL Tablets  
(1 x 10 mg)

From measured data  
Geometric Mean  
Arithmetic Mean (CV%)

Parameters	Teva-Bisoprolol	Monocor <sup>®**</sup>	Ratio of Geometric Means (%)	90 % Confidence Interval
AUC <sub>0-T</sub> (ng•h/mL)	668.929 676.770 (16)	679.161 686.178 (15)	98.49	95.32 - 101.78
AUC <sub>I</sub> (ng•h/mL)	699.499 708.579 (17)	711.558 720.356 (16)	98.31	95.02 - 101.71
C <sub>max</sub> (ng/mL)	42.562 42.880 (11)	43.588 43.784 (10)	97.65	94.98 - 100.39
T <sub>max</sub> * (h)	2.90 (39)	2.62 (25)	-	-
T <sub>1/2</sub> * (h)	10.19 (14)	10.29 (14)	-	-

\* expressed as arithmetic mean (CV%) only

\*\* Monocor<sup>®</sup> 10 mg Tablets manufactured by Biovail Pharmaceuticals, Canada; purchased in Canada

## **INDICATIONS AND CLINICAL USAGE**

TEVA-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.

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

## **CONTRAINDICATIONS**

TEVA-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 TEVA-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,  $\beta$ -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. TEVA-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 TEVA-BISOPROLOL when the two drugs are used concomitantly. The effects of  $\beta$ -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  $\beta$ -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, TEVA-BISOPROLOL therapy should be immediately withdrawn.

Abrupt Cessation of Therapy with TEVA-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  $\beta$ -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 TEVA-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 TEVA-BISOPROLOL should be reinstated, 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  $\beta$ -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  $\beta$ -

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  $\beta$ -blockade, may occur with the use of TEVA-BISOPROLOL. In such cases, the dosage should be reduced or TEVA-BISOPROLOL discontinued.

Thyrotoxicosis:

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

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

Therefore, in such patients from whom TEVA-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 TEVA-BISOPROLOL (bisoprolol fumarate).

### **Bronchospastic Disease:**

In general, patients with bronchospastic pulmonary disease should not receive  $\beta$ -blockers. However, because TEVA-BISOPROLOL (bisoprolol fumarate) is relatively  $\beta_1$ -selective, it may be used cautiously in patients with bronchospastic disease who do not respond to, or who cannot tolerate other antihypertensive treatment. Since  $\beta_1$ -selectivity is not absolute, the lowest possible dose should be employed, a  $\beta_2$ -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 TEVA-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 TEVA-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  $\beta$ -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, TEVA-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 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.

### 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. TEVA-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 TEVA-

BISOPROLOL is considered essential, then mothers should stop nursing.

Pediatric Use:

Safety and effectiveness in children have not been established.

Drug Interactions:

Other  $\beta$ -blocking Agents: TEVA-BISOPROLOL should not be combined with other  $\beta$ -blocking agents.

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

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

Antiarrhythmic Agents: TEVA-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  $\beta$ -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 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 TEVA-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 fumarate 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  $\beta$ -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 TEVA-BISOPROLOL (bisoprolol fumarate) without a physician'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  $\beta$ -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)**

<b><u>Body System/Adverse Experience</u></b>	<b><u>All Adverse Experiences</u></b> n (%)
Musculo-skeletal	
arthralgia	11 (2.7)
myalgia	7 (1.7)
muscle cramps	6 (1.5)
Central Nervous System	
dizziness	14 (3.5)
headache	44 (10.9)
paraesthesia	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 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)**

<u>Body System/Adverse Experience</u>	<u>All Adverse Experiences</u> n (%)
Musculo-skeletal	
arthralgia	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 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 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 experiences reported with bisoprolol fumarate 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  $\beta$ -blocker 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 TEVA-BISOPROLOL 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  $\beta$ -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 ( $\beta_2$  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 TEVA-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 TEVA-BISOPROLOL. However, complications of excess isoproterenol should not be overlooked.

## **DOSAGE AND ADMINISTRATION**

In the treatment of mild to moderate hypertension TEVA-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.

### **Elderly:**

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

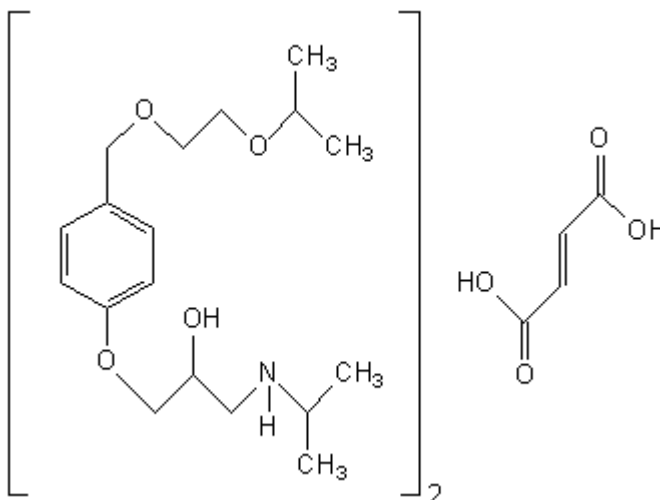
### **Children:**

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

**PHARMACEUTICAL INFORMATION****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:** 766.96 g/mol

**Physical form:** White to almost white crystalline powder

**Solubilities:** Very soluble in Water and in Methanol; freely soluble in chloroform, in glacial acetic acid, and in alcohol; slightly soluble in acetone and in ethyl acetate.

**pH Values:** pH of a 1% Solution: 6.0 - 7.0

**Dissociation Constants:**  $pK_{a1} = 8.95$  and  $pK_{a2} = 11.75$

Partial co-efficient: 0.129 (determined from a mixture of 50 mL of octanol and 50 mL of water containing 5% (w/v) of Bisoprolol Fumarate)

Melting Point: 100 - 103°C

Specific Rotation: Bisoprolol Fumarate is produced as a racemic mixture. The product is routinely tested for Optical rotation to a limit of  $-0.2^{\circ}$  to  $+0.2^{\circ}$ .

Composition:

Inactive ingredients: calcium phosphate, pregelatinized starch, microcrystalline cellulose, silicon dioxide, magnesium stearate, carnauba wax, hydroxypropyl methylcellulose, polyethylene glycol, polyoxyethylenesorbitan monooleate, and titanium dioxide. The 5 mg tablets also contain FD&C Red #40 AC Aluminum Lake and FD&C Yellow #6 FCF Aluminum Lake.

### **STABILITY AND STORAGE RECOMMENDATIONS**

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

### **AVAILABILITY OF DOSAGE FORMS**

TEVA-BISOPROLOL (bisoprolol fumarate) tablets are available in white plastic bottles containing 100 or 500 tablets.

The following strengths are available:

5 mg Tablet: Pink, film-coated, round, convex shaped tablets, debossed "5270" and "93" bisect on one side and plain on the reverse, each containing 5 mg of bisoprolol fumarate.

10 mg Tablet: White to off white colored, round, convex shaped tablets, debossed with "5271" above "93" on one side and plain on the reverse, each containing 10 mg of bisoprolol fumarate.

## **PHARMACOLOGY**

### **HUMAN PHARMACOLOGY**

$\beta_1$ -selectivity of bisoprolol fumarate has been demonstrated in both animal and human studies. No effects at therapeutic doses on  $\beta_2$ -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<sub>1</sub>) were observed with doses of bisoprolol fumarate 20 mg and higher, similar to the small increased in AWR also noted with the other cardioselective  $\beta$ -blockers. The changes induced by  $\beta$ -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  $\beta$ -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.

LD<sub>50</sub>'s of the S(-)-enantiomer in mice and rats were similar to or greater than LD<sub>50</sub>'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 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 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	<ul style="list-style-type: none"> <li>• Dose dependent increase in serum triglycerides at 60-540 mg/kg/day</li> <li>• Increased incidence of pulmonary phospholipidosis at <math>\geq 180</math> mg/kg/day. Changes were reversible following cessation of treatment</li> <li>• Adrenal cortical nodules observed in all of F</li> </ul>
Rat: Wistar-AF HAN/SPF	10	PO - Diet	0, 100, 150, 225, 350, 500	13	<ul style="list-style-type: none"> <li>• Increased heart weight, circumference and volume. Increased left ventricular volume and surface<sup>a</sup></li> <li>• Increased incidence of phospholipidosis <math>\geq 225</math> mg/kg/day</li> <li>• Adrenal cortical nodules observed in all treated F</li> </ul>
Rat: Wistar-AF HAN/SPF	25	PO - Gavage	0, 15, 50, 150	26 (with 4 wk recovery)	<ul style="list-style-type: none"> <li>• Dose dependent increase in serum triglycerides at 50 -150 mg/kg/day</li> <li>• Increased heart weight, volume and circumference. Increase in left ventricular volume and surface<sup>a</sup></li> <li>• Adrenal cortical nodules observed in all F</li> </ul>
Rat: Wistar-AF HAN/SPF	20	PO - Diet	0, 25, 75, 225	52 (with 13 wk recovery)	<ul style="list-style-type: none"> <li>• Increased heart weight, volume and circumference. Increase in left ventricular volume and surface<sup>a</sup></li> </ul>
Rat: Wistar-AF HAN/SPF	12	IV	0, 0.2, 1, 5	4 (with 4 wk recovery)	<ul style="list-style-type: none"> <li>• No drug related deaths or antemortem or post mortem findings</li> </ul>

**TABLE 4A: SUBACUTE AND CHRONIC TOXICITY: BISOPROLOL ALONE - (CONTINUED)**

Species/Strain	No./Sex/Dose	Route	Dose Group (mg/kg/day)	Duration (weeks)	Results
Dog: Beagle	3	PO - Capsule	0, 3, 10, 30, 100	4	<ul style="list-style-type: none"> <li>Tremors, lethargy and transient bradycardia at 100 mg/kg/day</li> <li>1 death at 100 mg/kg/day<sup>b</sup></li> <li>Salivation and vomiting up to 3 hrs post dosing at 100 mg/kg/day</li> </ul>
Dog: Beagle	8 6 6 8	PO - Capsule	0 10 27 73	26 (with 8 wks recovery)	<ul style="list-style-type: none"> <li>12 deaths at 73 mg/kg/day<sup>b</sup></li> <li>Salivation, vomiting, tremor, staggering and lethargy at <math>\geq 27</math> mg/kg/day</li> <li>Slight reduction in mean systolic BP and HR in all test groups</li> <li>Hepatocyte inclusion bodies at <math>\geq 27</math> mg/kg/day</li> </ul>
Dog: Beagle	6	PO - Capsule	0, 3, 10, 30	52 (with 8 wks recovery)	<ul style="list-style-type: none"> <li>1 death at 30 mg/kg/day<sup>b</sup></li> <li>Salivation and emesis up to 3 hours after dosing at 30 mg/kg/day</li> <li>Mean HR increase at all doses</li> <li>Hepatocyte inclusion bodies in control and test groups</li> </ul>
Dog: Beagle	2	IV	0, 1, 3, 10	4	<ul style="list-style-type: none"> <li>No death or toxicity</li> </ul>
Dog: Beagle	5 or 8	PO - Capsules	0, 3, 10, 30	52	<ul style="list-style-type: none"> <li>10 deaths at 30 mg/kg, 1 death at 10 mg/kg</li> <li>Salivation emesis, lacrimation, soft stool at all test doses</li> <li>Serum triglycerides increase in at all test doses</li> </ul>
Dog: Beagle	5 or 8	PO - Capsules	20, 30	52	<ul style="list-style-type: none"> <li>4 deaths at <math>\geq 20</math> mg/kg/day</li> <li>Prolonged PR interval, primary AV block and atrial and ventricular premature complexes in all surviving animals</li> <li>Salivation, emesis, lacrimation, soft stool in both test groups</li> <li>Increased serum triglycerides</li> </ul>

**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/day)	Duration (Weeks)	Results
Rat: Wistar-AF HAN/SPF	1 5 1 0	PO - Garage	0 10.5 (3+7.5) 35 (10+25) 105 (30+75) 7.5 (HCTZ alone) 75 (HCTZ alone)	26 (with 8 wks recovery)	<ul style="list-style-type: none"> <li>• HR decreased at 10:25 mg/kg/day</li> <li>• Burrowing and salivation at 10:25 and 30:75 mg/kg/day</li> <li>• Minimal focal myocardial necrosis<sup>a</sup> and/or fibrosis, with varying amounts of inflammatory infiltrates in control and treated males</li> <li>• 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</li> </ul>
Dog: Beagle	5	PO - Capsule	0 10.5 (3+7.5) 35 (10+25) 25 (HCTZ alone)	26 (with 8 wks recovery)	<ul style="list-style-type: none"> <li>• Slight decrease in the HR and slight prolongation of PQ interval at 3:7.5 and 10:25 mg/kg/day</li> <li>• Sporadic changes in organ weight</li> <li>• Increase in single cell hepatocellular necrosis seen at 10:25 mg/kg/day and HCTZ groups</li> <li>• Increase in binucleated hepatocytes in the 10:25 mg/kg/day group</li> <li>• Single cell hepatocellular necrosis was the only histopathological change seen after recovery</li> </ul>

- (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  
and Bisoprolol/Hydrochlorothiazide (1:2.5) Combination in Male Rats**

<b>Study</b>	<b>Summary Incidence of Myocardial Necrosis</b>			
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 Months Bisoprolol with 2 Months Recovery	3/10	3/10	0/10	3/10

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

<b>Study</b>	<b>Summary Incidence of Myocardial Necrosis</b>			
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**

<b>Summary Incidence of Myocardial Necrosis</b>				
<b>Group:</b>	<b>Control</b>	<b>Bisoprolol</b>	<b>Hydrochlorothiazide</b>	<b>Bisoprolol + Hydrochlorothiazide</b>
Dose (mg/kg) :	0	30	75	30 + 75
Incidence	5/20	8/20	6/20	12/10
<b>Group:</b>	<b>Control</b>	<b>Metoprolol</b>	<b>Hydrochlorothiazide</b>	<b>Metoprolol + Hydrochlorothiazide</b>
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  $\beta$ -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.

**BIBLIOGRAPHY**

1. Buhler FR, Berglund G, Anderson OK, Brunner HR, Scherrer U, van Brummelin P, Distler A, Philipp T, Fogari R, Mimran A, Fourcade J, dal Palu C, Prichard BNC, Backhouse CI, Reid JL, Elliott H, Zanchetti A. Double-blind comparison of the cardioselective  $\beta$ -blockers bisoprolol and atenolol in hypertension: the Bisoprolol International Multicenter Study (BIMS). *J Cardiovascular Pharmacol.* 1986; 8(Suppl. 11): S122-S127.
2. Chatterjee SS. The cardioselective and hypotensive effects of bisoprolol in hypertensive asthmatics. *J Cardiovascular Pharmacol.* 1986; 8(Suppl. 11): S74-S77.
3. Janka HU, Ziegler AG, Disselhoff G, Mehnert H. Influence of bisoprolol on blood glucose, glucosuria, and haemoglobin A1 in noninsulin-dependent diabetics. *J Cardiovascular Pharmacol.* 1986; 8(Suppl. 11):S96-S99.
4. Kirch W, Rose I, Klingmann I, Pabst J, Ohnhaus EE. Interaction of bisoprolol with cimetidine and rifampicin. *Eur J Clin Pharmacol.* 1986; 31:59 - 62.
5. Kirch W, Rose I, Demers HG, Leopold G, Pabst J, Ohnhaus EE. Pharmacokinetics of bisoprolol during repeated oral administration to healthy volunteers and patients with kidney or liver disease. *Clin Pharmacokin.* 1987; 13:110-117.
6. Neuss H, Conrad A, Mitrovic V, Schlepper M. Electrophysiologic effects of an acute  $\beta$ -blockade induced by bisoprolol in patients with supraventricular tachycardia as assessed by His-bundle electrograms. *J Cardiovascular Pharmacol.* 1986; 8(Suppl. 11):S167-S170.
7. Pfannenstiel P, Rummeny E, Baew-Christow T, Bux B, Cordes M, Adam W, Panitz N, Pabst J, Disselhoff G. Pharmacokinetics of bisoprolol and influence on serum thyroid hormones in hyperthyroid patients. *J Cardiovascular Pharmacol.* 1986; 8(Suppl. 11):S100-S105.
8. Tattersfield AE. Assessment of  $\beta$ -adrenoceptor selectivity of a new  $\beta$ -adrenoceptor antagonist, bisoprolol, in man. *Br J Clin Pharmacol.* 1984; 18:343 - 347.
9. Weiner L, Frithz G. Antihypertensive effects of bisoprolol during once daily administration in patients with essential hypertension; a dose-ranging study with parallel groups. *Eur J Clin Pharmacol.* 1986; 29:517 - 521.
10. Weiner L, Frithz G. Dose-effect relationship and long-term effects of bisoprolol in mild to moderate hypertension. *J Cardiovascular Pharmacol.* 1986; 8(Suppl. 11):S106-S112.
11. Zbinden, G. Pulmonary Lipidosis, in Progress in Toxicology Special Topics. New York, Springer Verlag. 1976; vol. II, pp 34 - 33.
12. Product monograph for Monacor<sup>®</sup>. Biovail Pharmaceuticals Inc., Mississauga, Ontario, Canada, October 11, 2002.

13. Product Monograph for Apo-Bisoprolol. Apotex Inc., Toronto, Ontario, Canada. Control # 197881, January 6, 2017.
14. A two-way, single-dose, crossover bioavailability study of two formulations of bisoprolol fumarate 10 mg tablets in healthy subjects under fasting conditions.

Completed November 22, 2003. Data on file at Teva Canada Limited.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION**

**PrTEVA-BISOPROLOL  
Bisoprolol Fumarate Tablets USP**

Read this carefully before you start taking **TEVA-BISOPROLOL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-BISOPROLOL**.

**What is TEVA-BISOPROLOL used for?**

TEVA-BISOPROLOL (bisoprolol fumarate) is used to treat mild to medium high blood pressure. It can be used alone or with other drugs to control blood pressure.

**How does TEVA-BISOPROLOL work?**

TEVA-BISOPROLOL is a type of medicine called a beta-blocker. It works by decreasing the blood pressure and reducing how hard the heart has to work.

**What are the ingredients in TEVA-BISOPROLOL?**

Medicinal ingredients: bisoprolol fumarate

Non-medicinal ingredients: calcium phosphate, pregelatinized starch, microcrystalline cellulose, silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polyoxyethylenesorbitan monooleate, titanium dioxide.

The 5 mg tablets also contain red and yellow iron oxide.

**TEVA-BISOPROLOL comes in the following dosage forms:**

Tablets: 5 mg (pink) and 10 mg (white).

**Do not use TEVA-BISOPROLOL if:**

- you are allergic to bisoprolol fumarate or any of the non-medicinal ingredients found in TEVA-BISOPROLOL.
- you are pregnant or plan to become pregnant, or if you are breast-feeding. You must stop breast-feeding before taking TEVA-BISOPROLOL.
- you have one of the following heart problems: heart failure or any other heart condition.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-BISOPROLOL. Talk about any health conditions or problems you may have, including if you:**

- have a history of heart failure.
- have asthma, bronchitis, emphysema, or other lung diseases.
- heart, kidney or liver disease.
- diabetes. TEVA-BISOPROLOL may hide some of the symptoms of diabetes.

- an overactive thyroid gland (hyperthyroidism). TEVA-BISOPROLOL may hide the symptoms of an overactive thyroid.
- will have an anaesthetic for surgery.
- have a history of allergic type reactions or are allergic to a many allergens.
- have a condition called peripheral artery disease. This means that your arteries are more narrow and don't carry blood to your legs as easily. Taking TEVA-BISOPROLOL may cause symptoms or make your symptoms worse.

**Other warnings you should know about:**Heart Failure

Patients taking beta-blockers can develop heart failure. Your doctor will check you for signs and symptoms of heart failure while you are taking TEVA-BISOPROLOL.

Stopping treatment with TEVA-BISOPROLOL

You should keep taking TEVA-BISOPROLOL until your doctor tells you to stop. Your doctor will tell you to slowly stop taking it over a two week period if and when it is time for you to stop.

Rash

You may develop a skin rash while taking TEVA-BISOPROLOL. Tell your doctor if your rash becomes severe.

Lowered heart rate

Your heart rate may lower while you are taking TEVA-BISOPROLOL. If it gets too low, your dose may be reduced or your doctor may tell you to stop taking TEVA-BISOPROLOL.

Allergic reactions

While you are taking TEVA-BISOPROLOL:

- a severe allergy reaction may be harder to treat.
- you may be more likely to have a severe allergic reaction.

Blood Tests

Your doctor will order regular blood tests for you while you are taking TEVA-BISOPROLOL. The blood tests will help monitor your blood cells, kidneys and liver.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. The following may interact with TEVA-BISOPROLOL:**

- Other beta-blocking Agents
- Reserpine or guanethidine (heart medications)
- Clonidine (high blood pressure medications)
- Verapamil, diltiazem, disopyramide (high blood pressure and heart medications)
- Fingolimod (immunosuppressant drugs)

- Rifampin (antibiotic): may cause TEVA-BISOPROLOL to work less effectively because it causes bisoprolol to leave the body quicker
- Common cold remedies and nasal drops: may cause an increase in blood pressure

**How to take TEVA-BISOPROLOL:**

- Take TEVA-BISOPROLOL **exactly** as your healthcare professional tells you.
- Do not miss doses or take extra doses, unless your healthcare professional tells you. If you are not clear about the directions, ask your healthcare professional or pharmacist. You may take TEVA-BISOPROLOL along with other medications to help control your blood pressure. Take these medications as prescribed.
- Take TEVA-BISOPROLOL once daily and at about the same time every day.
- Take TEVA-BISOPROLOL tablets whole. Do not chew or crush them.

**Usual dose:**

Your doctor will determine your dose. You will likely take 5 mg to 20 mg once a day.

Your healthcare professional will regularly monitor your condition. Your dose may change depending on how well TEVA-BISOPROLOL is working.

**Overdose:** If you think you have taken too much TEVA-BISOPROLOL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms

**Missed Dose:**

- If you miss a dose of TEVA-BISOPROLOL, take it as soon as you remember on the same day.
- Take your next dose at your usual time the next day.
- Do not take more than one dose of TEVA-BISOPROLOL at the same time to make up for a missed dose.

**What are possible side effects from using TEVA-BISOPROLOL?**

These are not all the possible side effects you may feel when taking TEVA-BISOPROLOL. If you experience any side effects not listed here, contact your healthcare professional. The most common side effects are:

- headache
- fatigue
- inflammation in the nose (rhinitis or sinusitis)
- diarrhea
- dizziness
- joint pain
- trouble sleeping
- nausea (feeling like vomiting)
- sore throat

- abdominal pain, indigestion
- back pain
- coughing

Tell your healthcare professional if:

- any of the side effects are serious or severe.
- you have any of the side effects for several days.

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 TEVA-BISOPROLOL with your healthcare professional or pharmacist. **Do not stop or restart TEVA-BISOPROLOL on your own.**

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
Aching muscles	✓		
<b>Allergic Reactions:</b> dizziness or trouble breathing, hot or itching skin, rashes, swelling.			✓
<b>Bronchitis:</b> cough, production of mucus, fatigue, shortness of breath, chest discomfort, slight fever	✓		
Chest pain		✓	
Depression		✓	
Diarrhea	✓		
<b>Difficulty breathing:</b> shortness of breath, stuffy nose, wheezing	✓		
Dizziness	✓		
Fatigue	✓		
Fever	✓		
Generalized body swelling		✓	
Hot flushes	✓		

<b>Impotence (in men):</b> trouble getting or keeping an erection		✓	
Joint pain		✓	
Muscle cramps	✓		
<b>Nerve pain: stabbing or burning pain</b>		✓	
Persistent noise in the ears	✓		
Swelling of hands, ankles or feet		✓	
Vision abnormality		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhpm/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### Storage:

- Store at room temperature 15°C-30°C.
- Keep out of sight and reach of children.

If you want more information about **TEVA-BISOPROLOL**:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer's website <http://www.tevacanada.com>; or by calling 1-800-268-4127 ext. 3; or email [druginfo@tevacanada.com](mailto:druginfo@tevacanada.com).

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