# Rx Bisoprolol Fumarate + Amlodipine Besilate Tablets

# Concor® AM 2.5/5

**Description**: Concor AM is a fixed dose combination of bisoprolol fumarate and amlodipine besilate. Bisoprolol fumarate is a white crystalline powder, approximately equally hydrophilic and lipophilic, and readily soluble in water, methanol, ethanol, and chloroform. Amlodipine besilate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol.

**Composition**:
Concor AM 2.5
Each film-coated tablet contains: Bisoprolol fumarate USP 2.5 mg, Amlodipine Besilate BP equivalent to Amlodipine base 5 mg.
Colours used: Brilliant Blue FCF, Ferric oxide USPNF (black), Ferric oxide USPNF (yellow), Titanium Dioxide BP.
Concor AM 5
Each film-coated tablet contains: Bisoprolol fumarate USP 5 mg, Amlodipine Besilate BP equivalent to Amlodipine base 5 mg.
Colours used: Titanium Dioxide BP

SCHEDULE H DRUG :Warning :To be sold by retail on the prescription of a Registered Medical Practitioner only.

**Clinical Pharmacology**:
Bisoprolol fumarate and amlodipine have been used individually and in combination for the treatment of hypertension.
Bisoprolol fumarate is a beta 1-selective (cardioselective) adrenoceptor blocking agent without significant membrane stabilizing or intrinsic sympathomimetic activities in its therapeutic dose range.
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.
**Pharmacokinetics**: Bisoprolol Fumarate. The absolute bioavailability after a 10 mg oral dose of bisoprolol fumarate is about 80%. The first pass metabolism of bisoprolol fumarate is about 20%. The pharmacokinetic profile of bisoprolol fumarate has been examined following single doses and at steady state. Binding to serum proteins is approximately 30%. Peak plasma concentrations occur within 2-4 hours of dosing with 2.5 to 20 mg, and mean peak values range from 9.0 ng/mL at 2.5 mg to 70 ng/mL at 20 mg. Once-daily dosing with bisoprolol fumarate results in less than twofold intersubject variation in peak plasma concentrations. Plasma concentrations are proportional to the administered dose in the range of 2.5 to 20 mg. The plasma elimination half-life is 9-12 hours and is slightly longer In elderly patients, in part because of decreased renal function. 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 half-life and once-daily dosing. Bisoprolol is eliminated equally by renal and nonrenal pathways with about 50% of the dose appearing unchanged in the urine and the remainder 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 faeces. The pharmacokinetic characteristics of the two enantiomers are similar. Bisoprolol 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 threefold compared to healthy subjects.
In patients with liver cirrhosis,the rate of elimination of bisoprolol is more variable and significantly slower than that in healthy subjects, with a plasma half-life ranging from 8 to 22 hours.
In elderly subjects, mean plasma concentrations at steady state are increased, in part attributed to lower creatinine clearance. However, no significant differences in the degree of bisoprolol accumulation is found between young and elderly populations.
Amlodipine Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food. The apparent volume of distribution of amlodipine is 21 L. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.
Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
**Pharmacodynamics**:
**Bisoprolol Fumarate.** Findings in clinical hemodynamics studies with bisoprolol fumarate are similar to those observed with other beta-blockers. The most prominent effect is the negative chronotropic effect, giving 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.
In normal volunteers, bisoprolol fumarate therapy resulted in a reduction of exercise and isoproterenol-induced tachycardia. The maximal effect occurred within 1-4 hours post-dosing. Effects generally persisted for 24 hours at doses of 5 mg or greater.
The mechanism of bisoprolol fumarate's antihypertensive effect has not been completely established. Factors that may be involved include:
1) Decreased cardiac output
2) Inhibition of renin released by the kidneys
3) Diminution of tonic sympathetic outflow from vasomotor centers in the brain.
Beta1-selectivity of bisoprolol fumarate has been demonstrated in both animal and human studies. No effects at therapeutic doses on beta2-adrenoreceptor density have been observed. Pulmonary function studies have been conducted in healthy volunteers, asthmatics, and patients with chronic obstructive pulmonary disease (COPD). Doses of bisoprolol fumarate ranged from 5 to 60 mg, atenolol from 50 to 200 mg, metoprolol from 100 to 200 mg, and propanolol from 40 to 80 mg. In some studies, slight, asymptomatic increases in airway resistance (AWR) and decreases in forced expiratory volume (FEV1) were observed with doses of bisoprolol fumarate 20 mg and higher, similar to the small increases in AWR noted with other cardioselective beta-blocking agents. The changes induced by beta-blockade with all agents were reversed by bronchodilator therapy.
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.
**Amlodipine** Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.
With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.
As with other calcium channel blockers hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.
Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or rnan. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.
**Clinical Studies**: In a study conducted by Mehta S and coworkers to evaluate the efficacy and tolerability of a fixed dose combination of amlodipine 5 mg and bisoprolol 2.5 mg in essential hypertension in 106 patients, at the end of 8 weeks, the mean systolic blood pressure was reduced from 163.4 ± 8. 23 mm Hg to 130.08 ± 8.5 mm Hg, diastolic blood pressure was reduced from 101.97 ± 4.3 mm Hg to 80.31± 4.89 mm Hg and the heart rate was reduced from 87.3 ± 11.07 beats per minute to 68.4 ± 8.13 beats per minute. The responder rate of 89% was recorded at the end of 8 weeks. The fixed dose combination of amlodipine 5 mg and bisoprolol 2.5 mg was well tolerated with 94% patients reporting excellent to good tolerability.
A post marketing study evaluating the efficacy and safety of bisoprolol 5 mg plus amlodipine 5 mg in essential hypertension in 801 patients with stage 2 hypertension for a period of 4 weeks, showed a reduction on systolic blood pressure from 171.9 ± 17.9 mm Hg to 134.3 ± 10.1 mm Hg. Diastolic blood pressure was reduced from 103.9 ± 9.6 mm Hg to 83.4 ± 6.2 mmHg. Heart rate was reduced from 83.3 ± 9.6 beats per minute to 74.6 ± 6.8 beats per minute. The responder rate at the end of 4 weeks of treatment was 82.5. Excellent to good efficacy and tolerability was observed in 91.4% and 90.3% of the subjects, respectively.
**Indications and Usage**: In the management of moderate-severe hypertension.
**Dosage**: One tablet once daily or as directed by the physician.
**Contraindications**: Cardiogenic shock, overt cardiac failure, second or third degree AV block, and marked sinus bradycardia and known sensitivity to amlodipine/ bisoprolol.
**Warnings**: **Bisoprolol**: Overt congestive cardiac failure, abrupt cessation of therapy, peripheral vascular disease, bronchospastic disease, anesthesia and major surgery, diabetes and hypoglycemia and thyrotoxicosis.
**Amlodipine**: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.
**Precautions**: **Bisoprolol**: Impaired Renal or Hepatic Function, Drug Interactions (other beta-blocking agents clonidine, myocardial depressants or inhibitors of AV conduction).
**Amlodipine**: Severe aortic stenosis, Congestive Heart Failure, and Hepatic Failure.
**Side-effects**: In the study conducted by Mehta S and coworkers to evaluate the efficacy and tolerability of a fixed dose combination of amlodipine 5 mg and bisoprolol 2.5 mg in essential hypertension in 106 patients, the most commonly reported adverse event was edema feet in 8% patients. Other adverse events reported were headache (4%), fatigue (3%), leg cramps (3%) and dry mouth (1%).
In the post marketing study evaluating efficacy and safety of bisoprolol 5 mg plus amlodipine 5 mg in essential hypertension in 801 patients with stage 2 hypertension the most common adverse events were edema feet (7.4%), headache (4.01%), fatigue (3.48%), leg cramps (2.8%) and dry mouth (0.81%). Other adverse events reported were gastric irritation, angina, asthma, cold extremities, cough, decrease in libido, dizziness, facial flushing, postural hypotension, skin rash, sleep disturbance and vertigo.
**Presentation**:
Concor AM 2.5 = Pack of 3 strips of 10 tablets. Reg, N° Lebanon 221711
Concor AM 5 = Pack of 3 strips of 10 tablets. Reg. N° Lebanon 221712
**Storage**: Store in a cool, dry and dark place.

Packed by **Pharmaline - Lebanon**
Licensed by **MERCK Ltd.,**
a subsidiary of **MERCK KGaA- Germany**

MERCK

To prevent misuse, please destroy container/carton after use.

Rev. 02/09 905034-A