BIOBETA™- AM

PRODUCT DESCRIPTION:

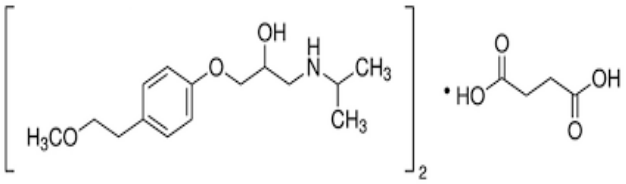
BIOBETA™- AM Tablets

Each film coated tablet contains,
Metoprolol Succinate IP – 50 mg (as Prolonged release)
Amlodipine IP – 5 mg
Excipients – q.s.

PHARMACEUTICAL DESCRIPTION:

Metoprolol Succinate:

Structural formula:



Structural formula

Molecular formula: $C_{34}H_{56}N_2O_{10}$

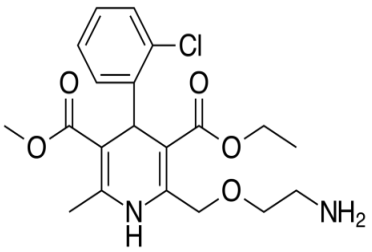
Chemical name: Di-(±)-1-(isopropylamine)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate

Molecular weight: 652.80 g/mol

Metoprolol succinate is a white, crystalline powder. It is freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane and 2-propanol, and practically insoluble in ethyl acetate, acetone, diethyl ether and heptane.

Amlodipine:

Structural formula:



Molecular formula: $C_{20}H_{25}ClN_2O_5$

Chemical name: 3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3, 5-dicarboxylate

Molecular weight: 408.879 g/mol

BIOBETA™- AM tablets are a fixed-dose combination of metoprolol prolonged-release, a selective Beta1-adrenoceptor antagonist, and amlodipine, a dihydropyridine calcium channel blocker.

PHARMACOLOGIC PROPERTIES:

PHARMACODYNAMICS

Metoprolol Succinate:

Metoprolol is a Beta1-selective (cardio selective) adrenergic receptor blocking agent, i.e. it blocks β_1-receptors at doses lower than those needed to block β_2-receptors. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases atrioventricular (AV) nodal conduction.

The beta-blocking activity of metoprolol in man by (1) reduction in the heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative beta1-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta2-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) significantly less than a nonselective beta-blocker, propranolol, at equivalent beta1-receptor blocking doses.

Beta-adrenergic receptor blockade is useful in the treatment of angina, hypertension, and heart failure there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta2-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Treatment with metoprolol produced an improvement in left ventricular ejection fraction. Metoprolol was also shown to delay the increase in left ventricular end-systolic and end- diastolic volumes after 6 months of treatment.

Hypertension: The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of

catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

Angina Pectoris: By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris.

Amlodipine:

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. 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.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (after load) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

Hemodynamics

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 pressures are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous (IV) 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 the heart rate or blood pressures in normotensive patients with angina.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in the glomerular filtration rate and effective renal plasma flow, without a change in the 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 heart failure patients with agents possessing significant negative inotropic effects.

Electrophysiologic Effects

Amlodipine does not change sinoatrial nodal function or AV conduction in intact animals or man. In patients with chronic stable angina, IV 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. Amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on 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.

PHARMACOKINETICS

Absorption

Metoprolol Succinate:

Absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following IV administration, indicating about 50% first-pass metabolism. The plasma metoprolol levels following administration of metoprolol succinate are characterized by lower peaks, longer time to peak

and significantly lower peak-to-trough variation. At steady state, the average bioavailability of metoprolol following administration of metoprolol succinate, across the dosage range of 50-400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. The bioavailability of metoprolol shows a dose-related, although not directly proportional, increase with dose and is not significantly affected by food following metoprolol succinate administration.

Amlodipine:

After oral administration of therapeutic doses of amlodipine, absorption produces peak plasma concentrations between 6-12 hours. Absolute bioavailability has been estimated to be between 64-90%. The bioavailability of amlodipine is not altered by the presence of food. Steady-state plasma levels of amlodipine are reached after 7-8 days of consecutive daily dosing.

Distribution

Metoprolol Succinate:

Metoprolol crosses the blood brain barrier and has been reported in the cerebral spinal fluid (CSF) at a concentration measuring 78% of the simultaneous plasma concentration. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. In comparison to conventional metoprolol, the plasma metoprolol levels following administration of metoprolol prolonged-release are characterized by lower peaks, longer time to peak and significantly lower peak-to-trough variation. The peak plasma levels following once-daily administration of metoprolol prolonged-release average one-fourth to one-half the peak levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses.

Amlodipine:

Approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Metabolism

Metoprolol Succinate:

When administered orally, it exhibits a stereoselective metabolism that is dependent on oxidation phenotype.

Amlodipine:

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Excretion

Metoprolol Succinate:

Elimination is mainly by biotransformation in the liver, and the plasma half-

life ranges from approximately 3-7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity.

Amlodipine:

Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours and 10% of the parent compound and 60% of the metabolites are excreted in the urine.

SPECIAL POPULATIONS:

Hepatic Impairment

Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{½}$) is 56 hours in patients with impaired hepatic function, titrate slowly when administering amlodipine to patients with severe hepatic Impairment.

Pediatric

The pharmacokinetic profile of metoprolol prolonged-release in pediatric hypertensive patients (6-17 years of age) receiving doses ranging from 12.5 to 200 mg once daily. The pharmacokinetics of metoprolol was similar to those described previously in adults. Age, gender, race and ideal body weight had no significant effects on metoprolol pharmacokinetics. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight. Metoprolol pharmacokinetics has not been investigated in patients. Doses of amlodipine between 1.25 mg and 20 mg. Weight- adjusted clearances and volume of distribution were similar to values in adults.

INDICATIONS:

BIOBETA™- AM tablets are indicated for:

- Hypertension
- Angina pectoris

CONTRAINDICATIONS:

BIOBETA™- AM Is contraindicated if,

Severe bradycardia, Second-or third-degree heart block, cardiogenic shock, de-compensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and in patients who are hypersensitive to any component of this product.

WARNING & PRECAUTIONS:

Drug Interactions:

Catecholamine Depleting Drugs (e.g. reserpine, MAO Inhibitors)

Catecholamine-depleting drugs may have an additive effect when given with beta-blocking agents. Observe patients treated with BIOBETA™- AM plus a catecholamine depletor should therefore be carefully observed for evidence

of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Drugs Inhibiting CYP2D6

Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, co-administration of quinidine 100 mg and immediate-release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, co-administration of propafenone 150 mg t.i.d with immediate-release metoprolol 50 mg t.i.d resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

CYP3A4 Inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when BIOBETA™- AM is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers

No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be closely monitored when BIOBETA™- AM is co-administered with CYP3A4 inducers.

Digitalis Glycosides

Both digitalis glycosides & beta-blockers slow AV conduction & decrease heart rate. Concomitant use can increase the risk of bradycardia.

Clonidine

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If co-administered, BIOBETA™- AM tablets should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine with BIOBETA™- AM tablets, the introduction of BIOBETA™- AM tablets should be delayed for several days after clonidine administration has been stopped.

Calcium Channel Blockers

Concomitant use of calcium channel blockers with beta-blockers can increase the risk of bradycardia. Because of significant inotropic and chronotropic effects in patients treated with beta-blockers and calcium channel blockers of the verapamil and diltiazem type, caution should be exercised in patients treated with these agents concomitantly.

General

Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, phenytoin, indomethacin, non-steroidal anti-inflammatory drugs, cimetidine, magnesium and aluminum hydroxide antacid, atorvastatin, simvastatin, sildenafil, grapefruit juice, ethanol antibiotics and oral hypoglycemic drugs.

Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Beta-Blocker Withdrawal

Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Ischemic Heart Disease

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris, and in some cases, myocardial infarction have occurred. When discontinuing chronically administered BIOBETA™- AM, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1-2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, BIOBETA™- AM should be reinstated promptly, and measures appropriate for the management of unstable angina should be taken. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing BIOBETA™- AM in patients treated only for hypertension.

Bronchospastic Diseases

Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta1- selectivity, however, BIOBETA™- AM may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Because beta1-selectivity is not absolute, use the lowest possible dose of BIOBETA™- AM. Bronchodilators, including beta2-agonists, should be readily available or administered concomitantly.

Major Surgery

Avoid initiation of a high-dose regimen of prolonged-release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with

cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Diabetes and Hypoglycemia

Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

Peripheral Vascular Disease

Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Anaphylactic Reaction

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

Pheochromocytoma

If BIOBETA™- AM is used in the setting of pheochromocytoma; it should be given in combination with an alpha-blocker, and only after the alpha-blocker has been initiated. Administration of beta-blockers alone in the setting of pheochromocytoma has been associated with a paradoxical increase in blood pressure due to the attenuation of beta- mediated vasodilation in skeletal muscle.

Heart Failure

Worsening cardiac failure may occur during up-titration of BIOBETA™- AM. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of BIOBETA™- AM. It may be necessary to lower the dose of BIOBETA™- AM or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of BIOBETA™-AM.

Renal Impairment

The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. No reduction in dosage is needed in patients with chronic renal failure. The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Hepatic Impairment

No studies have been performed with metoprolol prolonged-release in patients with hepatic impairment. Because metoprolol prolonged-release is metabolized by liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. It is recommended to initiate metoprolol prolonged-release therapy at lower doses than those recommended for a given indication; and increase doses gradually. Also, amlodipine is extensively metabolized by the liver and the plasma elimination half-life is 56 hours in patients with impaired hepatic impairment. Hence, BIOBETA™- AM tablets should be used with caution in patients with hepatic impairment.

Use in Pregnancy:

Metoprolol: Category C
Amlodipine: Category C

There are no adequate and well controlled studies in pregnant women. Hence, BIOBETA™- AM tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation:

Metoprolol is excreted in breast milk in very small quantities. It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while BIOBETA™- AM tablets are administered.

Pediatric Use:

Safety and effectiveness of BIOBETA™- AM tablets in pediatric patients has not been established in patients.

Geriatric Use:

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE EFFECTS:

Metoprolol Succinate:

The following are the adverse reactions:

- Worsening angina or myocardial infarction
- Worsening heart failure
- Worsening AV block

Hypertension and Angina: Most adverse reactions have been mild and transient. The most common (>2%) adverse reactions are tiredness, dizziness, depression, diarrhea, shortness of breath, bradycardia and rash.

Heart Failure: In the MERIT-HF study comparing metoprolol in daily doses up to 200 mg (mean dose 159 mg once-daily; n=1990) to placebo (n=2001), 10.3% of metoprolol patients discontinued for adverse reactions vs. 12.2% of placebo patients.

The table below lists adverse reactions in the MERIT-HF study that occurred at an incidence of ≥ 1% in the metoprolol and greater than placebo by more than 0.5%, regardless of the assessment of causality.

Table: Adverse reactions occurring in the MERIT-HF study at an incidence ≥1% in the metoprolol and greater than placebo by more than 0.5%

	Metoprolol	Placebo
	N=1990 % of patients	N=2001 % of patients
Dizziness/vertigo	1.8	1.0
Bradycardia	1.5	0.4
Accident and/or injury	1.4	0.8

Post-Operative Adverse Events:

In a randomized, double-blind, placebo-controlled trial of 8351 patients with or at risk for atherosclerotic disease undergoing non-vascular surgery and who were not taking beta-blocker therapy, metoprolol 100 mg was started 2 to 4 hours prior to surgery then continued for 30 days at 200 mg per day.
Metoprolol use was associated with a higher incidence of bradycardia (6.6% vs. 2.4%; HR 2.74; 95% CI 2.19, 3.43), hypotension (15% vs. 9.7%; HR 1.55; 95% CI 1.37, 1.74), stroke (1.0% vs. 0.5%; HR 2.17; 95% CI 1.26, 3.74) and death (3.1% vs. 2.3%; HR 1.33; 95% CI 1.03, 1.74) compared to placebo.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of metoprolol prolonged release. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension

Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia

Respiratory: Wheezing (bronchospasm), dyspnea

Gastrointestinal: Nausea, dry mouth, constipations, flatulence, heartburn, hepatitis, vomiting

Hypersensitive Reactions: ruritis

Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance

Potential Adverse Reactions: In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol prolonged-release.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, clouded sensorium and decreased performance on neuropsychometrics

Hematologic: Agranulocytosis, non-thrombocytopenic purpura, thrombocytopenic purpura

Hypersensitive Reactions: Laryngospasm, respiratory distress

Amlodipine:

Post-Marketing Experience

Where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural hypotension, postural dizziness, vasculitis

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo

Gastrointestinal: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia

General: allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease

Musculoskeletal System: arthralgia, arthrosis, muscle cramps, myalgia

Psychiatric: sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization

Respiratory System: dyspnea, epistaxis

Skin and appendages: angioedema, erythema multiforme, pruritis, rash, rash erythematous, rash maculopapular

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain & tinnitus

Urinary System: micturition frequency, micturition disorder, nocturia

Autonomic Nervous System: dry mouth, increased sweating

Metabolic and Nutritional: hyperglycemia, thirst

Hemopoietic: leucopenia, purpura, thrombocytopenia

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory test. No clinically relevant changes are noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen or creatinine.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliable estimate their frequency or establishes a causal relationship to drug exposure.

The following post-marketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In post-marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, coronary heart disease, peripheral vascular disease, diabetes mellitus and abnormal lipid profiles.

DOSAGE AND ADMINISTRATION:

Dosage should be individualized. The recommended initial dose is one tablet of BIOBETA™- AM is once daily. If necessary, the dose may be increased to two tablets once daily.

Small, fragile or elderly individuals or patients with hepatic insufficiency can be initiated on separate tablets of metoprolol prolonged-release and amlodipine 2.5 mg both once daily.

The dose of amlodipine can be increased to 5 mg once daily depending on the patient tolerability. When the patient is stabilized on this dose he/she can be shifted to one tablet of BIOBETA™- AM 50 once daily.

A patient whose blood pressure is not adequately controlled with metoprolol prolonged-release or amlodipine monotherapy may be switched to the combination therapy.
For convenience, patients receiving metoprolol prolonged-release and amlodipine from separate formulations may instead wish to receive a combination formulation containing the same component doses.

OVERDOSAGE:

Metoprolol Succinate:

Signs and Symptoms

Overdosage of metoprolol prolonged-release may lead to severe bradycardia, hypotension and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment

Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol, however metoprolol is not highly protein bound.

Bradycardia: Administer IV atropine; repeat to effect. If the response is inadequate, consider IV isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.

Hypotension: Treat underlying bradycardia, Consider IV vasopressor infusion, such as dopamine or norepinephrine Bronchospasm: Administer a beta2-agonist, including albuterol inhalation, or an oral theophylline derivative

Cardiac Failure: Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider IV dobutamine, isoproterenol or glucagon

Amlodipine:

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.
If massive amlodipine overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support

including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. As amlodipine is highly-protein bound, hemodialysis is not likely to be of benefit.

STORAGE CONDITION: Store below 25°C in cool, dry & dark place. Protect from light and Keep out of reach of children.

PRESENTATION: Metoprolol Succinate 50mg PR + Amlodipine 5mg Tablets

PACKING: 1*10 TAB.

For the use only of a Registered Medical Practitioner or Hospital or a Laboratory

BIOS LAB PVT. LTD.
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