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

BETACARD -AM

(Amlodipine And Atenolol Tablets)

COMPOSITION

Each uncoated bilayered tablet contains :

Amlodipine Besilate I.P. equivalent to
Amlodipine 5 mg
Atenolol I.P. 50 mg
Colour : Red Oxide of Iron

DESCRIPTION

Amlodipine and Atenolol tablets combine two antihypertensive agents, a ß1 blocker namely Atenolol and a long acting third generation calcium channel blocker Amlodipine besylate.

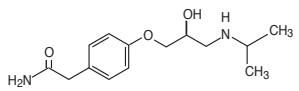
Atenolol, a synthetic, ß1 selective (cardio-selective) adrenoreceptor-blocking agent, may be chemically described as phenylacetamide, 4-[2'-hydroxy 3'-[(1-methylethyl) amino] propoxy]. The besilate salt of amlodipine is a long acting calcium channel blocker. It is chemically described as 3-ethyl 5methyl-2-(2-amino-ethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate.

Although blood pressure lowering is possible with more or less all anti-hypertensive drugs available on the market, it is advantageous to use combination therapy. Beta blockers are logical therapeutic option in patients with angina pectoris, because they reduce myocardial oxygen consumption by their negative inotropic and negative chronotropic effects. The use of optimally dosed beta blockade is preferred, but is also limited in anginal patients because of well-known contraindications of beta blockade or the occurrence of adverse side effects. Amlodipine is a dihydropyridine calcium antagonist with a high bioavailability, a slow onset of action, and a long elimination half-life of about 35 to 50 hours, allowing once daily dosage The combination of dihydropyridines and with beta blockers is an effective approach in the treatment of angina, aiming at a combination of 2 pharmacologic goals: reduction in myocardial oxygen consumption and an increase in myocardial oxygen supply.

CLINICAL PHARMACOLOGY

Atenolol

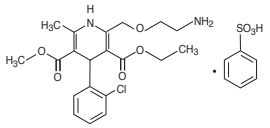
Atenolol is (RS)-4-(2-hydroxy -3-isopropylamino propoxy) phenylacetamide. Atenolol is a white or almost white powder. It is soluble in ethanol sparingly soluble in water, slightly soluble in dichloromethane; practically insoluble in ether. Atenolol empirical formula is $C_{14}H_{22}N_2O_3$ and its molecular weight is 266.3.



Atenolol is ß1 selective (cardioselective) beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympath-omimetic (partial agonist) activities. This preferential effect is not absolute, however, and at higher doses, atenolol inhibits ß2 adrenoreceptors, chiefly located in the bronchial and vascular musculature. Atenolol works by competing for receptor sites on, in atenolol's case, cardiac muscle. This slows down the strength of the heart's contractions and reduces its oxygen requirements and the volume of blood it has to pump. Hypertension (high blood pressure) may be treated with these drugs because of their ability to increase the diameter of the blood vessels thus allowing blood to flow under less pressure. Beta-blockers are also used to treat Myocardial infarction (heart attack) and Arrhythmias (rhythm disorders), angina (chest pains), and disorders arising from decreased circulation and vascular constriction, including migraine.

Amlodipine

Amlodipine Besilate is 3-ethyl 5-methyl(4RS)-2-[(2-(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene sulphonate. Amlodipine Besilate is white or almost white powder. It is slightly soluble in water, freely soluble in methanol; sparingly soluble in ethanol (95 %); slightly soluble in 2-propanol. Amlodipine Besilate empirical formula is $C_{26}H_{31}ClN_2O_8S$ and its molecular weight is 567.1.



Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the trans-membrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that Amlodipine binds to both dihydropyridine and non-dihydropyridine 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 s.c. 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

Atenolol

Following oral administration, about 50 to 60 % of an Atenolol dose is absorbed with maximum plasma concentrations reached within 2 to 4 hours. Atenolol is widely distributed in the body (although only a small proportion of an administered dose reaches the brain), and readily crosses the placenta. In adult patients with normal renal function the elimination half-life is about 5 to 7 hours and total clearance is about 6 L/h (100 ml/min) per 1.73m2. A shorter elimination half life (4.5 hours) has been observed in children. However, there are wide intra and interindividual differences in the pharmacokinetic properties of Atenolol. Most absorbed Atenolol is excreted unchanged in the urine. Accumulation into breast milk has been reported but plasma concentrations are negligible in infants. In patients with renal dysfunction the elimination rate is decreased and related to glomerular filtration rate.

Amlodipine

After oral administration of therapeutic doses of Amlodipine, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of Amlodipine is not altered by the presence of food. 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. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination 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. The pharmacokinetics of Amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose. Elderly patients and patients with hepatic insufficiency have decreased clearance of Amlodipine with a resulting increase in AUC of

approximately 40-60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

INDICATIONS

Atenolol and Amlodipine tablets are indicated for the treatment of moderate to severe hypertension and all grades of angina, unresponsive to Atenolol or Amlodipine monotherapy.

CONTRAINDICATIONS

It is contraindicated in patients who are hypersensitive to Atenolol or Amlodipine.

Atenolol

Atenolol is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, overt cardiac failure and metabolic acidosis. Caution must be exercised with the use of atenolol in patients with: asthma, bronchitis, chronic respiratory disease, and bradycardia of less than 50 beats/min, peripheral vascular disease and Raynauds syndrome.

Amlodipine

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 Amlodipine is administered. Safety and effectiveness in Pediatrics has not been established. No overall differences in effectiveness or safety were observed between elder and younger patients but greater sensitivity of some older individuals cannot be ruled out. Since amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amlodipine to patients with severe hepatic impairment. In general, calcium channel blockers should be used with caution in patients with heart failure.

USE IN PREGNANCY, LACTATION AND CHILDREN

Atenolol

Atenolol can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of atenolol, starting in the second trimester of pregnancy, has been associated with the birth of infants that are small for gestational age. No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus Atenolol is excreted in human breast milk at a ratio of1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when atenolol is administered to a nursing woman. Safety and effectiveness in pediatric patients have not been established

Amlodipine

There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to fetus. 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 amlodipine is administered. Safety and effectiveness of amlodipine in children have not been established.

ADVERSE EFFECTS

Fixed dose combination of Atenolol and Amlodipine is well tolerated. Adverse events have been limited to those that were reported previously with Atenolol and/or Amlodipine. Adverse events are generally mild and transient in nature and do not require discontinuation of therapy. The most serious adverse effects with atenolol are heart failure, heart block, and bronchospasm. Other more minor side effects include fatigue and coldness of extremities. Reactions tend to be more severe after intravenous injection as opposed to oral administration. The most commonly reported adverse effects with amlodipine are headache, flushing, hypotension, nausea, abdominal pain, edema/swelling, palpitation, back pain, dizziness, cough, asthenia or fatigue, rash. Rarely angioedema, first dose hypotension, transient elevation of liver transaminases and hyperkalaemia.

DRUG INTERACTIONS

Atenolol

The pharmacokinetic parameters of atenolol were unchanged by either concomitant administration of nifedipine and nicardipine.In contrast, following coadministration of verapamil, hydrochlorthiazide, ampicillin and antipyrine decreased the pharmacokinetic parameters. Indomethacin may reduce the effect of ß-blockers. Administration of calcium salts decreases the bioavailability of atenolol. Concomitant use of atenolol with verapamil may cause increased incidence of heart block.

Amlodipine

In vitro data in human plasma indicate that Amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of Amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time. In clinical trials, Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

DOSAGE AND ADMINISTRATION

The usual starting dose of Atenolol and Amlodipine is 1 tablet once daily with a maximum dose of two tablets once daily.

OVERDOSAGE

Atenolol

Overdosage with atenolol has been reported with patients surviving acute doses as high as 5g. One death was reported in man who may have taken as much as 10g acutely.The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause and bradycardia.Additionally, common effects like congestive heart failure, hypotension, bronchospasm and/or hypoglycemia might also be expected.

Amlodipine

Excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia might be expected with amlodipine overdosage. In humans, experience with intentional overdosage of Amlodipine is limited though few cases have been reported. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. As Amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store in a dry place at a temperature not exceeding 30ºC, protected from light.
Keep all medicines out of reach of children

PRESENTATION

BETACARD AM is available in a blister pack of 10 tablets

torrent

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Vill. Bhud & Makhnu Majra, Baddi-173 205,
Teh. Nalagarh, Dist. Solan (H.P.), INDIA.