AMLOCI-AT
Amlodipine & Atenolol Tablets

COMPOSITION

Each uncoated tablet contains:

Amlodipine Besilate	BP	
eq. to Amlodipine		5 mg
Atenolol	BP	50 mg
Excipients		q. s.

DESCRIPTION:

AMLOCI-AT contains Amlodipine & Atenolol used to treat hypertension.

PHARMACODYNAMIC PROPERTIES

Amlodipine:

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Atenolol

Atenolol is a beta-blocker, which is $beta_1$-selective, (i.e. acts preferentially on $beta_1$-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

Atenolol is without intrinsic sympathomimetic and membrane-stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear.

It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

It is unlikely that any additional ancillary properties possessed by S(-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

PHARMACOKINETIC PROPERTIES

Amlodipine:

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%.

The bioavailability of amlodipine is not affected by food intake.

Distribution

The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine

Elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing.

Atenolol

Absorption

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Distribution

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Elimination

The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

THERAPEUTIC INDICATIONS

- Essential Hypertension
- Angina Pectoris

POSOLOGY AND METHOD OF ADMINISTRATION

The recommended dosage is one tablet of AMLOCI-AT daily. If necessary, the dosage may be increased to two tablets daily. The dosage however should be individualized.

Special Populations

Patients with Renal Impairment

Dosage of AMLOCI-AT should be adjusted in cases of severe impairment of renal function. Dosage of atenolol should not exceed 50 mg/day when creatinine clearance is 15-35 ml/min/1.73 m^2. While in patients with creatinine clearance <15 ml/min/1.73 m^2, the maximum dosage of atenolol should be 25 mg/day.

Patients with Hepatic Impairment

The recommended initial dose in patients with hepatic impairment is half tablet of AMLOCI-AT.

Elderly Patients (65 years or above)

Dose selection for an elderly patient should be cautious, usually starting at half tablet of AMLOCI-AT.

Method of administration

For oral administration only.

Swallow the whole tablet with a glass of water. Do not crush, chew, or break it.

CONTRAINDICATIONS

Hypersensitivity to either component, cardiogenic shock, uncontrolled heart failure, sick sinus syndrome, second-or third-degree heart block, untreated phaeochromocytoma, metabolic acidosis, bradycardia (<45 bpm), hypotension, and severe peripheral arterial circulatory disturbances.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Amlodipine

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 and/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.

Patients with Hepatic Failure

Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, titrate slowly when administering amlodipine to patients with severe hepatic impairment.

Atenolol

Precautions

General

Patients already on a beta-blocker must be evaluated carefully before atenolol is administered. Initial and subsequent dosages can be adjusted downward depending on clinical observations, including pulse and blood pressure. Atenolol may aggravate peripheral arterial circulatory disorders.

Patients with Renal Impairment

Atenolol Tablets should be used with caution in impaired renal function.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Warnings

Cardiac Failure

Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure.

In patients with acute myocardial infarction, cardiac failure that is not promptly and effectively controlled by 80 mg of IV furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

Concomitant Use of Calcium Channel Blockers

Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise when beta-blockers are administered with verapamil or diltiazem. Patients with pre-existing conduction abnormalities or left ventricular dysfunction are particularly susceptible.

Bronchospastic Diseases

Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of its relative $beta_1$ selectivity, however, atenolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, the lowest possible dose of atenolol should be used with therapy initiated at 50 mg and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Diabetes and Hypoglycaemia

Atenolol should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycaemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses, atenolol does not potentiate insulin-induced hypoglycaemia and, unlike non-selective beta-blockers, does not delay recovery of blood glucose to normal levels.

Untreated Pheochromocytoma

Atenolol should not be given to patients with untreated pheochromocytoma.

Pregnancy and Fetal Injury

Atenolol Tablets can cause fetal harm when administered to a pregnant woman. Atenolol crosses the placental barrier and appears in cord blood. Administration of the combination, 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 the combination 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.

Neonates born to mothers who are receiving atenolol at parturition or breast-feeding may be at risk for hypoglycaemia and bradycardia. Caution should be exercised when atenolol are administered during pregnancy or to a woman who is breast-feeding.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

AMLODIPINE+ATENOLOL is known to interact with potassium-sparing diuretics (amiloride, eplerenone, spironolactone), anti-depression medication (lithium), high blood pressure-lowering pills (benazepril, metoprolol, ramipril, hydrochlorothiazide), drugs used to control lipid levels in the blood (atorvastatin, simvastatin), medicines to treat erectile dysfunction (sildenafil), antibiotics (clarithromycin, erythromycin, rifampin), antifungal (itraconazole, ketoconazole), anti-HIV drugs (ritonavir), anti-epilepsy medicines (carbamazepine, phenytoin, phenobarbital, primidone), immune-suppressing drugs (cyclosporine, tacrolimus) and painkillers (ibuprofen, aspirin).

PREGNANCY AND LACTATION

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Breast-feeding

AMLODIPINE & ATENOLOL can pass through the breast milk and harm the baby, so it should not be taken while breastfeeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Caution is recommended, especially at the start of treatment with the combination.

UNDESIRABLE EFFECTS

- Nausea
- Sleepiness
- Ankle swelling
- Headache
- Palpitations
- Cold extremities
- Flushing (sense of warmth in the face, ears, neck, and trunk)
- Slow heart rate
- Edema (swelling)
- Constipation
- Tiredness

OVERDOSE

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 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, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein-bound, haemodialysis is not likely to be of benefit.

Atenolol

The predominant symptoms reported following atenolol overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic-blocking agent and which might also be expected in atenolol overdose are congestive heart failure, hypotension, bronchospasm and/or hypoglycaemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. Atenolol can be removed from the general circulation by haemodialysis.

SHELF LIFE

36 Months

PACKAGING

10 Tablets are packed in Alu-Alu blister and such 3 blisters are packed in a printed carton along with pack insert.

STORAGE CONDITION

Store in cool & dry place, below 30°C. Protect from light.

Keep the medicine out of reach of children.

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