# AMIPIN 5 mg TABLET

**FORMULA:** Each tablet contains; Amlodipine besilate equivalent to 5 mg of Amlodipine.

**PHARMACOLOGICAL PROPERTIES:**

**Pharmacodynamic properties:**

Amlodipine, active substance of AMIPIN, 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 and correspondingly decreases in peripheral vascular resistance and reduction in blood pressure. Experimental data suggest that Amlodipine binds both to dihydropyridine and non-dihydropyridine binding sites. Contraction periods of heart muscle and vascular smooth muscles are dependent on transfer of extracellular calcium ions via specific ion channels into intracellular environment. In patients with hypertension, therapeutic doses amlodipine provides vasodilatations with resultant reductions of blood pressure in both the supine and standing positions. In chronic dosing, such decreases in blood pressure are not accompanied by significant alterations in heart pace or plasma catecholamine levels. Plasma concentrations are associated with effect in both in young and elderly patients. In hypertensive patients with normal kidney functions, therapeutic doses of Amlodipine caused decrease in renal vascular resistance and an increase in glomerular filtration rate, efficient renal plasma flow was constituted without a change in filtration fraction or proteinurea. In patients treated with Amlodipine with normal ventricle function, hemodynamic cardiac function measurements during rest and exercise (or pace control), like in other calcium channel blockers, without causing a significant effect on dP/dt or left ventricle end diastolic pressure or volume, generally causes a small increase in cardiac index. In hemodynamic studies, even if Amlodipine is given to patients with beta blockers, does not cause a negative inotropic effect as long as administered to humans and animals within therapeutic dose range. Amlodipine does not alter sinoatrial nodal function or atrioventricular conduction in healthy humans and animals. In clinical studies, where Amlodipine was given in combination with beta blockers to patients with hypertension or angina, no adverse effects on electrocardiographic parameters were noted. Amlodipine has been proven to have beneficial effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary arterial disease.

**Pharmacokinetic properties:**

**Absorption:** After oral administration of solely therapeutic doses, amlodipine reaches peak plasma concentrations between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. 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 in patients with hypertension.
**Biotransformation:** Amlodipine is extensively (approximately 90%) metabolized by the liver to inactive metabolites.
**Elimination:** Plasma elimination of Amlodipine is biphasic and terminal elimination half life is approximately 30-50 hours. Steady state plasma concentrations are reached in 7-8 days following constant intake. 10% of parent compound and 60% of Amlodipine metabolites are excreted via urine.
**Linearity:**
Amlodipine expresses linear pharmacokinetics.

**Characteristic Properties in Patients**

**Kidney/Liver Insufficiency**

Pharmacokinetics of Amlodipine is not significantly affected by kidney insufficiency. Therefore, in patients with mild to moderate kidney insufficiency may receive conventional initial doses. In patients with liver failure, Amlodipine clearance is reduced with a resultant 40-60% increase in AUC. The drug should therefore be administered with caution in these patients.

**Pediatric**

There is no pharmacokinetic data available for pediatric population.

**Geriatric**

Time elapsed until occurrence of peak plasma concentrations of Amlodipine is similar in young and elderly patients. In elderly, Amlodipine clearance has a tendency to decrease, thus causing an increase in AUC and elimination half life.

**INDICATIONS:**

AMIPIN is indicated in treatment of hypertension and can be administered as monotherapy as well as in combination with other antihypertensive drugs.
AMIPIN is indicated for treatment of chronic stable angina pectoris and can be administered as monotherapy as well as in combination with other antianginal agents.
AMIPIN is indicated for treatment both in definitely diagnosed or suspected vasospastic angina pectoris (Prinzmetal's or variant angina). For this reason, this drug can be administered as monotherapy as well as in combination with other antianginal agents.

**CONTRAINDICATIONS:**

AMIPIN is contra-indicated in patients with a known hypersensitivity to dihydropyridines or to any of the excipients in the tablet.
This drug is contraindicated in cardiogenic shock, clinically significant aortic stenosis, and unstable angina (excluding Prinzmetal's angina).

**WARNINGS / PRECAUTIONS:**

**General:** Because the vasodilator effect sets on slowly, it's rare to see hypotension following oral intake of Amlodipine. However just like any other vasodilator agent, AMIPIN® should not be used in patients with advanced stage aortic stenosis.
**Cardiac Insufficiency:** Amlodipine did not cause any harmful effects in patients with NYHA class III-IV heart failure. In general, calcium antagonists should be used with precaution in patients with heart failure.
**Beta-blocker Discontinuation:** Amlodipine is not a beta-blocker and does not provide protection against danger caused by sudden beta-blocker discontinuation. Beta-blockers should be discontinued slowly with a gradual dose decreasing manner.
**Hepatic Impairment:** Plasma elimination half-life of amlodipine is prolonged in patients with impaired liver function (Child Pough A, B, C). AMIPIN® should be administered with caution in these patients.
**Renal Impairment:** Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialyzable.
**Use in pediatrics:** Safety and efficacy of Amlodipine in pediatric patients is not determined.

**Use in pregnancy and lactation:**

**Use in pregnancy:** Pregnancy category is C. Amlodipine can only be used in pregnancy only if benefits for the mother overcome potential risks for the fetus.
**Use in lactation:** It's not yet known whether amlodipine is excreted in mother milk. It's advised that breastfeeding mothers should either stop breastfeeding or discontinue amlodipine treatment.

**Effects on ability to drive and use machines:**

AMIPIN has no known effect on driving and using machines.

**DRUG INTERACTIONS:**

Amlodipine has been safely administered with thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, non-steroidal anti-inflammatory agents, steroids, antibiotics, and oral hypoglycemic drugs.
In vitro data from studies indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin and indometacin.
Co-administration of Amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers. Co-administration of Amlodipine with cimetidine did not alter the pharmacokinetics of Amlodipine. Co-administration of Amlodipine does not significantly alter the effect of warfarin on prothrombin response time. **Grapefruit juice:** In a study with 20 healthy volunteers, 240 ml grapefruit juice was consumed with a single oral dose of 10 mg Amlodipine, which had no effect on pharmacokinetics of amlodipine.
**Sildenafil:** When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.
**Cyclosporine:** Pharmacokinetic studies with cyclosporine have demonstrated that Amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

**SIDE EFFECTS/ ADVERSE EFFECTS:**

Adverse events that have been observed and reported in amlodipine trials are categorized below:
Very common (≥10%); common (≥1% to <10%); uncommon (≥0.1% to <1%); rare (≥0.01% to <0.1%) and very rare (<0.01%)

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**Blood and the Lymphatic System Disorders:**
Very rare : Thrombocytopenia

**Immune System Disorders:**
Very rare : Allergic reaction

**Metabolism and Nutritional Disorders:**
Very rare : Hyperglycemia

**Psychiatric Disorders:**
Uncommon : Mood changes, insomnia

**Nervous System Disorders:**
Common : Somnolence, dizziness, headache
Uncommon : Tremor, taste perversion, syncope, hypoesthesia, paraesthesia
Very rare : Peripheral neuropathy

**Eye Disorders:**
Uncommon : Visual disturbances

**Ear and Labyrinth Disorders:**
Uncommon : Tinnitus

**Cardiac Disorders:**
Common : Palpitations
Very rare : Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

**Vascular Disorders:**
Common : Flushing
Uncommon : Hypotension
Very rare : Vasculitis

**Respiratory, Thoracic and Mediastinal Disorders:**
Uncommon : Rhinitis, dyspnea
Very rare : Coughing

**Gastrointestinal System Disorders:**
Common : Abdominal pain, nausea
Uncommon : Vomiting, dyspepsia, altered bowel habits, dry mouth
Very rare : Pancreatitis, gastritis, gingival hyperplasia

**Hepatobiliary Disorders:**
Very rare : Hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)

**Skin and Subcutaneous Tissue Disorders:**
Uncommon : alopecia, purpura, skin discoloration, increased sweating, pruritus, rash.
Very rare : angioedema, erythema multiforme, urticaria

**Musculoskeletal and Connective Tissue Disorders:**
Uncommon : arthralgia, myalgia, muscle cramps, back pain

**Renal and Urinary Disorders:**
Uncommon : micturition disorder, nocturia, increased urinary frequency

**Reproductive System and Breast Disorders:**
Uncommon : impotence, gynaecomastia

**General Disorders and Administration Site Conditions:**
Common : oedema, fatigue
Uncommon : chest pain, asthenia, pain, malaise

**Investigations:**
Uncommon : weight increase, weight decrease

**IF YOU NOTICE ANY UNUSUAL EFFECTS, CONTACT TO YOUR DOCTOR.**

**POSOLOGY AND METHOD OF ADMINISTRATION:**
For hypertension the usual initial dose is 5mg Amlodipine once daily which may be increased to a maximum dose of 10mg per day. In patients with petite and weak posture, in elderly and in patients with impaired liver functions (Child Pough A, B, C) the initial dose must be 2.5 mg daily. In case AMIPIN is added to a treatment with other antihypertensive drugs, again 2.5 mg daily is recommended.
The dose is adjusted according to patient's response. The titration should be adjusted in 7-14 day intervals. However if the patient can be seen more often, dose adjustment may be done more frequently.
The recommended dose for chronic stable and vasospastic angina pectoris treatment is 5-10 mg twice daily. 5 mg doses are for elderly and patients with liver failure. 10 mg doses are required for vast majority of patients.

**OVERDOSE AND PRECAUTIONS:**
There are no experimental documents present regarding Amlodipine overdose. However, according to data in hand, it's possible to note extreme periferic vasodilatation and resultant prominent and possibly prolonged systemic hypotension. Hypotension due to Amlodipine over dosage calls for frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Since Amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

**SPECIAL PRECAUTIONS FOR STORAGE:**
Keep out of sight and reach of children and in its package.
Store at room temperature below 25°C.

**FORM OF PRESENTATION AND CONTENTS OF THE CONTAINER:**
AMIPIN 5 mg Tablet, in blister packs containing 20 and 30 tablets

**OTHER PHARMACEUTICAL DOSAGE FORMS:**
AMIPIN 10 mg Tablet, in blister packs containing 20 and 30 tablets

**PRODUCT LICENCE HOLDER :**
The holder of trade mark and Marketing Authorization is
**"BIOACTIVE T, UNITED KINGDOM.**

BioActiveT
United Kingdom

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