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

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Amlodipine Tablets IP
(Brand Name: ANGICAM® 2.5 / 5 Tablets)

2. Qualitative and Quantitative Composition

Each uncoated tablet contains:
Amlodipine Besylate IP equivalent to Amlodipine …….. 2.5 mg / 5 mg.
Excipients ……. q.s.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Amlodipine 2.5 mg and 5 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

ANGICAM Tablets are indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily stroke and myocardial infarction (MI).
ANGICAM Tablets are also indicated for the symptomatic treatment of chronic stable angina and vasospastic (Prinzmetal's) angina. It may be used alone or in combination with other antianginal agents.

4.2Posology and Method of Administration

For oral administration.
Recommended Dosage in Hypertension
Adults: Initially 5 mg of amlodipine to be administered once daily. Dosage to be up-titrated to maximum 10 mg once daily if blood pressure goal is not achieved within 4 weeks.
Elderly Individuals or Patients with Hepatic Insufficiency: Initial starting dose is 2.5 mg once daily. Adjust dosage according to blood pressure goals.
Children between 6 to 18 Years: The recommended starting dose is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in paediatric patients.
Or, as prescribed by the physician.

Recommended Dosage in Angina

Adults: The recommended dose for chronic stable or vasospastic angina is 5 to 10 mg once daily, with the lower dose suggested for the elderly and for patients with hepatic insufficiency. Most patients will require daily 10 mg dose for adequate effect.

Or, as prescribed by the physician.

4.3Contraindications

ANGICAM Tablets are contraindicated in the following conditions:

- Hypersensitivity to amlodipine or to any component of the formulation.
- Cardiogenic shock.
- Severe hypotension.
- Heart failure after acute myocardial infarction.
- Unstable angina.
- Significant aortic stenosis.
- Acute porphyria.

4.4Special Warnings and Precautions for Use

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 (CAD).

Patients with Hepatic Failure: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) is 56 hours in patients with impaired hepatic function. Thus, caution should be exercised and dose should be titrated slowly in patients with severe hepatic impairment.

4.5Drug Interactions

Impact of Other Drugs on Amlodipine

Sildenafil: Hypotensive effect is enhanced when amlodipine is given with sildenafil. Monitor for hypotension when these drugs are given together.

CYP3A Inhibitors (e.g., Ketoconazole, Itraconazole, Diltiazem, Erythromycin, Fluconazole, etc.): Co-administration with CYP3A inhibitors results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers (e.g., Carbamazepine, Phenytoin, Rifampin, etc.): No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure and edema should be closely monitored when amlodipine is co-administered with CYP3A inducers.

Impact of Amlodipine on Other Drugs

Simvastatin: Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immunosuppressants: Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of blood levels of cyclosporine and tacrolimus and dosage adjustment (whenever appropriate) is recommended.

4.6Use in Special Populations

Pregnant Women

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Thus, use of ANGIAM Tablets in pregnancy is only recommended when there is no safer alternative available and when the disease itself carries greater risk for the mother and foetus.

Lactating Women

Limited available data from a published clinical study reports that amlodipine is present in human milk. However, no adverse effects of amlodipine on the breastfed infant have been observed. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Patients

Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.
Thus, ANGICAM Tablets are not recommended in children below 6 years of age.

Geriatric Patients

Elderly patients with normal hepatic function may be given the same dose as recommended for adults. However, in the elderly patients, dosage increment (up-titration) should be done with caution.

4.7Effect on Ability to Drive and Use Machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8Undesirable Effects

Most common adverse reactions reported with amlodipine are headache and pedal edema. Adverse effects with an incidence >1% in clinical studies included abdominal pain, nausea, dizziness, somnolence, flushing, palpitations, and fatigue.

Rare adverse events observed in controlled clinical trials or open trials or post-marketing surveillance studies (causal relationship is uncertain) included:

Cardiovascular: Arrthythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural hypotension, vasculitis, cardiac failure, pulse irregularity, extrasystoles.
Central and Peripheral Nervous System: Hypoesthesia, peripheral neuropathy, paresthesia, tremor, vertigo, ataxia, hypertonia, migraine, apathy, agitation, amnesia.
Gastrointestinal: Anorexia, constipation, dysphagia, diarrhea, flatulence, gastritis, increased appetite, loose stools, pancreatitis, vomiting, gingival hyperplasia/hypertrophy.
Musculoskeletal System: Arthralgia, arthrosis, muscle cramps, myalgia, muscle weakness, twitching.
Psychiatric: Sexual dysfunction, insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System: Dyspnea, epistaxis, cough, rhinitis.
Skin and Appendages: Rash, pruritus, urticaria, angioedema, skin dryness, alopecia, skin discoloration.
Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, abnormal visual accommodation, xerophthalmia, tinnitus, parosmia, taste perversion.
Urinary System: Increased micturition frequency, nocturia, dysuria, polyuria.
Autonomic Nervous System: Dry mouth, increased sweating, cold and clammy skin.
Metabolic and Nutritional: Hyperglycemia, thirst.
Hemopoietic: Leukopenia, purpura, thrombocytopenia.
General: Allergic reaction, back pain, hot flushes, malaise, pain, rigors, weight gain, weight loss.

4.9Overdose

Overdose might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdose 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, hemodialysis is not likely to be of benefit.

5. Pharmacological Properties

5.1 Mechanism of Action

Amlodipine is a dihydropyridine class of long-acting calcium channel blocker – CCB (calcium antagonist). Amlodipine inhibits the transmembrane influx of calcium ions (Ca^{++}) 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. Serum calcium concentration is not affected by amlodipine.

5.2Pharmacodynamic Properties

Antihypertensive 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.

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.

With chronic once daily oral 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 intensity of elevated blood pressure at baseline (prior to treatment).

Thus, individuals with moderate hypertension (diastolic pressure 105 to 114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90 to 104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

Exertional Angina

In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works, 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 A2 analogs 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.

5.3Pharmacokinetic Properties

Absorption: After oral administration of therapeutic doses, amlodipine produces peak plasma concentrations between 6 to 12 hours. Absolute bioavailability has been estimated to be between 64 to 90%. The bioavailability is not altered by the presence of food.

Distribution: The volume of distribution is approximately 21 l/kg. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Metabolism: 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.
Excretion: Excretion from the plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.
The pharmacokinetics of amlodipine is 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 to 60%. Therefore, a lower initial dose may be required. A similar increase in AUC has been observed in patients with moderate to severe heart failure.

6. Nonclinical Properties

6.1 Animal Toxicology

Carcinogenesis: Rats and mice treated with amlodipine in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug.
Mutagenesis: Mutagenicity studies conducted with amlodipine revealed no drug related effects at either the gene or chromosome level.
Impairment of Fertility: There was no effect on the fertility of rats treated orally with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times [based on body weight of 50 kg] the maximum recommended human dose of 10 mg/day on a mg/m^2 basis).
Teratogenicity: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the maximum recommended human dose based on body surface area, respectively) during their respective periods of major organogenesis. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

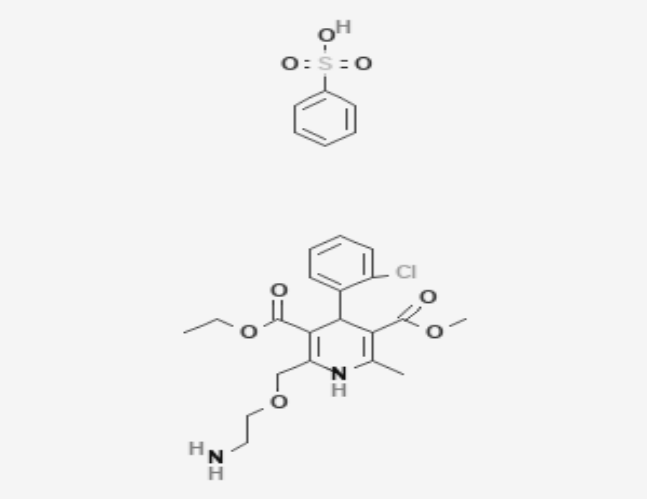
7. Description

ANGICAM 2.5 Tablets are off-white, circular, flat, beveled uncoated tablet with breakline between A and B engraved on one side and plain on other side.

ANGICAM 5 Tablets are white to off-white, circular, biconvex uncoated tablet with “5” engraved on one side and plain on other side.

ANGICAM 2.5 Tablets contains 2.5 mg of amlodipine whereas ANGICAM 5 Tablets contains 5 mg of amlodipine for oral administration in adults.

Amlodipine Besilate is the besilate salt of amlodipine. Amlodipine is a long-acting calcium channel blocker (CCB) of a synthetic dihydropyridine class with antihypertensive and antianginal effects.
Amlodipine besilate is a white crystalline powder.
Molecular Weight: 567.1 g/mol.
Molecular Formula: C20H25CIN2O5•C6H6O3S.
Chemical Name: 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2- chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate.
Structural Formula:



Inactive ingredients (excipients) of ANGICAM 2.5 Tablets contain Dibasic Calcium Phosphate, Starch, Purified Water, Sodium Starch Glycolate, Talc, Colloidal Silicon Dioxide, and Magnesium Stearate.

Inactive ingredients (excipients) of ANGICAM 5 Tablets contain Dibasic Calcium Phosphate, Starch, Microcrystalline Cellulose, Polyvinyl Pyrrolidone K-30, Purified Water, Colloidal Silicon Dioxide, and Magnesium Stearate.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 months.

8.3Packaging Information
Strip of 15 tablets.

8.4Storage and Handling Instructions
Store protected from light and moisture at a temperature not exceeding 25°C.
Keep out of reach of children.

9. Patient Counseling Information
Administration Instructions to Patients

- Instruct patients to take this medicine exactly as prescribed by doctor. Do not change the dose or stop therapy without consulting doctor.
- Instruct patients to take ANGICAM Tablets once a day, with or without food. It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose at a time.
- If patients miss a dose, they can take it as soon as they remember. Do not take ANGICAM Tablets if it has been more than 12 hours since the last missed dose. Wait and take the next dose at regular scheduled time.
- Patients should be advised to avoid this medicine during pregnancy and lactation.
- Use of this medicine is not recommended in children less than 6 years of age.
- Patients should be informed that while taking ANGICAM Tablets do not stop taking other prescription medicines, including any other blood pressure medicines, without consulting their doctor.

10. Details of Manufacturer
Blue Cross Laboratories Pvt. Ltd.
A – 12, MIDC, Ambad, Nashik – 422 010 Maharashtra.

11. Details of Permission or LicenseNumber with Date
Angicam 2.5 Tablet: Mfg. Lic. No.: BD/25; Date of FDA Product Permission: 07/01/2004.
Angicam 5 Tablet: Mfg. Lic. No.: BD/25; Date of FDA Product Permission: 07/01/2004.

12. Date of Revision
March 2021.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
A-12, M.I.D.C., NASHIK-422 010.
Regd. Off.: Peninsula Chambers, G. K. Marg, Mumbai-400 013.