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

Metoprolol Succinate Prolonged-release and Amlodipine Tablets IP
(Brand Name: ANGICAM®-M Tablets)

2. Qualitative and Quantitative Composition

Each Uncoated Bilayered Tablet Contains:
Metoprolol Succinate IP ……. 47.5 mg.
equivalent to Metoprolol Tartrate …… 50 mg.
(as prolonged-release form)
Amlodipine Besylate IP equivalent to Amlodipine ……..…….. 5 mg.
Excipients ……... q.s.
Colour: Lake Sunset Yellow FCF.

3. Dosage Form and Strength

Dosage Form: Tablets.
Dosage Strength: Amlodipine 5 mg and metoprolol tartrate 50 mg per tablet.

4. Clinical Particulars

4.1 Therapeutic Indication

ANGICAM-M Tablets are indicated for the treatment of essential hypertension not adequately controlled by monotherapy with either drug. In stage 2 hypertensive cases, ANGICAM-M Tablets can be administered as initial therapy.

4.2Posology and Method of Administration

For oral administration.
Adults: The usual initial dosage is 1 tablet once daily. If blood pressure goal is not achieved within 4 weeks, the dose may be increased to 2 tablets once daily. The dosage, however, should be individualized.
Amlodipine is effective in doses between 2.5 mg to maximum 10 mg once daily.
Metoprolol succinate is effective in doses between 25 mg to 100 mg once daily.
ANGICAM-M Tablets can be administered with or without food.
Do not crush or chew the tablet. Take whole tablet with water.
Or, as prescribed by the physician.

4.3Contraindications

ANGICAM-M Tablets are contraindicated in the following:

- Hypersensitivity to amlodipine or to metoprolol or to any component of this formulation.
- Severe bradycardia.
- Uncontrolled heart failure.
- Hypotension.
- Unstable angina.
- Sick sinus syndrome.
- Second or third degree atrioventricular (AV) block.
- Cardiogenic shock.
- Metabolic acidosis.
- Severe peripheral arterial disease.

4.4Special 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 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.

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.

Metoprolol

Abrupt Cessation of Therapy: 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 metoprolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of 1 to 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate metoprolol, and take measures appropriate for the management of unstable angina. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing in patients treated for hypertension.

Bronchospastic Disease: Patients with bronchospastic diseases should, in general, not receive beta-blockers. Because of its relative beta-1 cardio-selectivity, metoprolol may be used in patients with bronchospastic disease who do not respond to, or cannot tolerate, other anti- hypertensive treatment.

Major Surgery: Avoid initiation of a high-dose regimen of extended-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.

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.

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

4.5Drug Interactions

Amlodipine

1. 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.

2. 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.

Metoprolol

Catecholamine Depleting Drugs: Catecholamine-depleting drugs (e.g., reserpine, monoamine oxidase inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with metoprolol plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

CYP 2D6 Inhibitors: Drugs that inhibit CYP 2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration.

Digitalis, Clonidine, and Calcium Channel Blockers: Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta-blockers can increase the risk of bradycardia. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped.
Insulin and Oral Hypoglycemic Drugs: In diabetic patients who use insulin, beta-blocker treatment may be associated with increased or prolonged hypoglycaemia. Beta-blockers may also antagonize the hypoglycemic effects of sulfonylureas. The risk of either effect is less with a beta-1 selective drug such as metoprolol than with a non-selective beta-blocker. However, diabetic patients receiving metoprolol should be monitored to ensure that diabetes control is maintained.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Concurrent treatment with NSAIDs such as indomethacin may decrease the antihypertensive effect of metoprolol.

4.6Use in Special Populations

Pregnant Women

Amlodipine and Metoprolol Succinate: Pregnancy Category C. Animal studies have revealed no evidence of impaired fertility or teratogenicity. However, there are no adequate and well-controlled studies in pregnant women. Because, animal reproduction studies are not always predictive of human response, ANGICAM-M Tablets can be used during pregnancy only if clearly needed and when there is no safer alternative available.

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. Metoprolol is also excreted in the breast milk. It is advised that the nursing mother not breastfeed her child. Accordingly, 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

Safety and efficacy of this formulation in paediatric population is not known. Thus, ANGICAM-M Tablets are not indicated for use in children.

Geriatric Patients

Elderly patients have decreased clearance of amlodipine with a resulting increase in area under the plasma drug concentration-time curve (AUC) to approximately 40 to 60%. With metoprolol, there are no notable differences in efficacy or the rate of adverse reactions between older and younger patients. In general, a lower initial starting dose is recommended in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and/or other drug therapy. Dosage up-titration, if required, should be done with caution.

Renal Impairment Patients

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

Hepatic Impairment Patients

Amlodipine is extensively metabolized by the liver. Patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC up to 60%. A similar increase in AUC has been observed in patients with moderate to severe heart failure.

As metoprolol is metabolized by the liver, metoprolol blood levels are likely to be increased substantially with poor hepatic function.

Therefore, caution should be exercised and a lower starting dose to be used in patients with impaired hepatic function.

4.7Effect on Ability to Drive and Use Machines

As with all beta-blockers, metoprolol may affect patients' ability to drive and operate machinery. Amlodipine can have minor or moderate influence on the ability to drive and use machines. It should be taken into account that occasionally dizziness or fatigue may occur. If affected, patients should avoid driving or operating machinery or engaging in other tasks that require mental alertness.

4.8Undesirable Effects

Amlodipine

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/loss.

Metoprolol

Clinical Trials Experience

Most adverse reactions have been mild and transient. The most commonly (>2%) reported adverse reactions are tiredness, accident and/or injury, dizziness, vertigo, depression, diarrhea, shortness of breath, bradycardia, and rash.

Post-Marketing Experience

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.
Respiratory: Wheezing (bronchospasm), dyspnea.
Central Nervous System: Confusion, short-term memory loss, headache, somnolence, nightmares, insomnia, anxiety/nervousness, hallucinations, paresthesia.
Gastrointestinal: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.
Hypersensitive Reactions: Pruritus.
Miscellaneous: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, sweating, photosensitivity, taste disturbance.

4.9Overdose

Amlodipine

Symptoms: Overdose might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly reflex tachycardia. In humans, experience with intentional overdose of amlodipine is limited.
Treatment: 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.

Metoprolol

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

If any of the following conditions occur, general treatment should include:

- Bradycardia: Administer intravenous atropine; repeat the dose if efficacy is adequate. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.
- Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.
- Bronchospasm: Administer a beta-2 agonist, including albuterol inhalation, or an oral theophylline derivative.
- Cardiac Failure: Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider intravenous dobutamine, isoproterenol, or glucagon.

5. Pharmacological Properties

5.1 Mechanism of Action

Amlodipine

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.

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.

Metoprolol

Metoprolol is a beta-1 receptor (cardioselective) blocking agent. The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed as follow:

1. Competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output.
2. Central effect leading to reduced sympathetic outflow to the periphery.
3. Suppression of renin activity.

5.2Pharmacodynamic Properties

Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Metoprolol

Metoprolol is an antihypertensive agent with selective beta-1 receptor antagonist effect. 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 AV nodal conduction.

5.3Pharmacokinetic Properties

Amlodipine

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.

Metoprolol

Absorption: Absorption of metoprolol is rapid and complete. Bioavailability after oral administration of metoprolol is 50%, indicating about 50% first-pass metabolism.

Distribution: Metoprolol crosses the blood-brain barrier and has been reported in the CSF. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin.
Metabolism: Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP 2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype.
Excretion: Excretion is mainly by biotransformation in the liver, and the plasma half-life ranges from 3 to 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.

6. Nonclinical Properties

6.1 Animal Toxicology

Amlodipine

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.

Metoprolol

Carcinogenesis: Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day (41 times, on a mg/m^2 basis, the daily dose of 200 mg for a 60-kg patient), there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia.

In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day (18 times, on a mg/m² basis, the daily dose of 200 mg for a 60-kg patient), benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

Mutagenesis: All genotoxicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

Impairment of Fertility: No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient.

Teratogenicity: Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m² basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity.

7. Description

ANGICAM-M Tablets are light orange and white coloured, capsule shaped, biconvex, plain on both the sides and uncoated bilayered tablets.

ANGICAM-M Tablets contains 5 mg of amlodipine and 50 mg of metoprolol for oral administration in adults.

Amlodipine Besylate

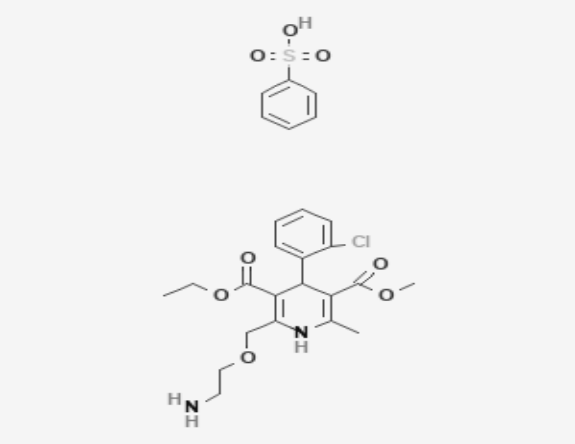
Amlodipine besylate is the besylate salt of amlodipine. Amlodipine is a long-acting calcium channel blocker (CCB) of a synthetic dihydropyridine class with antihypertensive and antianginal effects. Amlodipine besylate is a white crystalline powder.

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:



Metoprolol Succinate

Metoprolol succinate is the succinate salt form of metoprolol. Metoprolol is a cardioselective competitive beta-1 adrenergic receptor antagonist with antihypertensive properties.

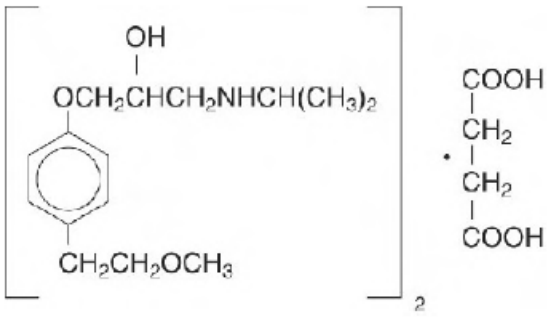
Metoprolol succinate is a white crystalline powder.

Molecular Weight: 652.8 g/mol.

Molecular Formula: C34H56N2O10.

Chemical Name: (±)1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol succinate (2:1) (salt).

Structural Formula:



Inactive ingredients (excipients) of ANGICAM-M Tablets contain Dibaisc Calcium Phosphate, Microcrystalline Cellulose, Colour Sunset Yellow FCF Lake, Polyvinyl Pyrrolidone, Isopropyl Alcohol, Sodium Starch Glycolate, Magnesium Stearate, Xanthan Gum, Methocel K 100 M, Hydroxy Propyl Cellulose, Colloidal Silicon Dioxide, and Sodium Stearyl Fumarate.

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.
Do not crush or chew the tablet. Take Whole tablet with water.

9. Patient Counseling Information
Instructions to Patients

- Instruct patients to take this medicine regularly and continuously as prescribed by your doctor. Do not change the dose or stop therapy without consulting doctor.
- Take ANGICAM-M Tablets once a day. 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.
- Advise patients to take this medicine, preferably with or immediately following meals. Do not crush or chew the tablet.
- If patients miss a dose, they can take it as soon as they remember. Do not take ANGICAM-M Tablets if it has been more than 12 hours since the last missed dose. Wait and take the next dose at regular scheduled time.
- It is advised to avoid this medicine during pregnancy and lactation.
- Use of this medicine is not recommended in children.
- Advise patients to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy has been determined.
- If any difficulty in breathing occurs, patients to contact their physician immediately.
- Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

10. Details of Manufacturer
Pure & Cure Healthcare Pvt. Ltd.
(A Subsidiary of Akums Drugs & Pharmaceuticals Ltd.)
Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar – 249403, Uttarakhand.

11. Details of Permission or License Number with Date

Mfg. Lic. No. : 31/UA/2013; Date of FDA Product Permission: 23/01/2018.

12. Date of Revision

April 2021.

Marketed 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.