



## A Review on Amlodipine Besylate

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### ABSTRACT:

1.4 billion people worldwide suffer from hypertension, which is the biggest cause of death. Among the popular calcium channel blockers that are utilized as treatment alternatives is amlodipine, a dihydropyridine with special qualities that set it apart from other medications in this class. The goal of this review is to present a current summary of the data that has been used to support amlodipine use over the last 30 years and to emphasize the drug's benefits for the cardiovascular system in the treatment of hypertension. Amlodipine's extended half-life (35–50 h) and low renal clearance (7 mL/min/mg) enable it to maintain its anti-hypertensive effect for over 24 hours after a single dose. Furthermore, even in the event of a missed dose, blood pressure (BP) management is preserved, offering ongoing protection against unintentional noncompliance. It has been demonstrated to successfully lower BP and lessen BP fluctuation. Amlodipine also lowers blood pressure without impairing renal or glycemic function in individuals with diabetes, chronic kidney disease, or systolic/diastolic blood pressure of 130/80 mm Hg or greater. Amlodipine is also a smart option for senior citizens because of its capacity to regulate blood pressure and guard against myocardial infarction and stroke. Edema, palpitations, vertigo, and flushing are among the side effects of amlodipine that are more frequent at the greater dose of 10 mg. Amlodipine is expected to be less expensive than typical care and is a cost-effective treatment.

**Keywords:** amlodipine, blood pressure variability, calcium channel blockers, hypertension

### INTRODUCTION

Hypertension is the leading cause of death worldwide, affecting 31.1% of the adult population (1.4 billion people).-It accounts for about half of all heart disease- and stroke-related deaths worldwide. The residual lifetime risk for developing hypertension is 90% for middle-aged or older individuals.

In recent decades, hypertension management has seen the introduction of several new principles/technologies. Advances in information technology have revolutionized hypertension monitoring with the development of new devices.-Current global guidelines recommend treating hypertension based on 24-h ambulatory blood pressure monitoring (ABPM) and home blood pressure (BP) measurements rather than measurement in the clinical setting. Additionally, observational studies and clinical trials reported that short- and long-term.

Amlodipine is a calcium channel blocker drug used to treat high blood pressure and coronary artery disease. It is marketed under several trade names, including Norvasc. It is consumed orally. Nausea, edema, fatigue, and stomach pain are typical adverse effects. Heart attacks and low blood pressure are examples of serious adverse effects. It's uncertain if using this product while pregnant or nursing is safe. Doses should be decreased in older patients and those with liver disease.

Amlodipine partially acts by enlarging the arteries. It is a dihydropyridine-type long-acting calcium channel blocker.

Amlodipine received FDA approval for medical use in 1990 after being invented in 1982. It is included in the List of Essential Medicines by the World Health Organization. It can be purchased as a generic drug. With more than 69 million prescriptions written for it in 2020, it was the fifth most prescribed drug in the US.

Amlodipine is used to treat hypertension and coronary artery disease in individuals who do not have heart failure and who have either vasospastic angina, which happens in cycles, or stable angina, which generally occurs after physical or mental stress.

It can be used as combination therapy or monotherapy to treat coronary artery disease or hypertension. Adults and children from 6 to 17 can both receive amlodipine.

Amlodipine and other calcium channel blockers may offer better stroke prevention than other blood pressure-lowering drug types.

Amlodipine and other calcium channel blockers are regarded as the first line of treatment for Raynaud's phenomenon when it comes to pharmaceutical management.

The Norvasc patent was protected by Pfizer's patent until 2007, at which point it completely expired. There are several generic versions accessible.

Amlodipine tablets in the UK may come from several sources and include varying salt compositions. The amlodipine base, or the amount of the tablet without the salts, is used to describe the tablet strength. As a result, tablets with various salt contents are regarded as interchangeable. There are other fixed-dose combinations of the angiotensin converting enzyme inhibitor perindopril and the dihydrodipine

Besylate, mesylate, or maleate are the forms available in medicine. Amlodipine besylate has a molecular weight of 567.1 and is a white, crystalline powder. It dissolves somewhat in ethanol and hardly marginally in water. For oral use, Amlodipine Besylate Tablets are designed as white tablets containing 2.5, 5 and 10 milli grams of amlodipine.

Each tablet has the following inactive ingredients in addition to the active ingredient, amlodipine besylate: magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and dibasic calcium phosphate dihydrate.

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## REVIEW OF LITERATURE

**Aakanksha Sharma et al.**, The article "Development and Characterization of Amlodipine Besylate" by Aakanksha Sharma et al. claims that One well-known risk factor for cardiovascular disorders is hypertension, and the first class of antihypertensive medications is calcium channel blockers. As a member of the dihydropyridine family, amlodipine besylate is well-known for its ability to effectively treat hypertension. Their goal was to create a microsphere that may be utilized to treat hypertension, thereby reducing the frequency of dose, increasing bioavailability, and lowering the likelihood of side effects. Using solvent evaporation procedures, the microsphere was created, and it was then examined for pre- and post-formulation research. Studies conducted before and after formulation both produced positive findings. In post-formulation investigations, formulation F8 produced the most favourable and good outcomes in terms of swelling index, percentage yield, drug entrapment research, and particle size determination. 92% of formulation F8's medication content is acceptable, and the stability research produced positive findings as well. As a result, a stable and optimal microsphere formulation was created.

**Saumitra Roy et al** ,The effectiveness of amlodipine in clinical trials is covered in an article titled "Effectiveness of Amlodipine on Hypertension" by Saumitra Roy et al. Through a retrospective analysis of electronic medical record data of adult patients diagnosed with essential hypertension ( $\geq 140/90$  mmHg) and prescribed amlodipine as monotherapy or add-on therapy, their aim is to provide practical evidence regarding the efficacy of amlodipine as monotherapy or in combination with other antihypertensive drugs (AHDs) in Indian patients. The number of AHD classes prescribed at the time amlodipine was started was used to categorise the patients. The primary objective was the change in both the diastolic and systolic blood pressures from baseline (DBP and SBP). Assessing the percentage of patients who met treatment objectives in accordance with the 2018 guidelines from the European Society of Cardiology and the European Society of Hypertension served as the secondary endpoint. Before starting amlodipine therapy and after at least one month of treatment, readings were taken.

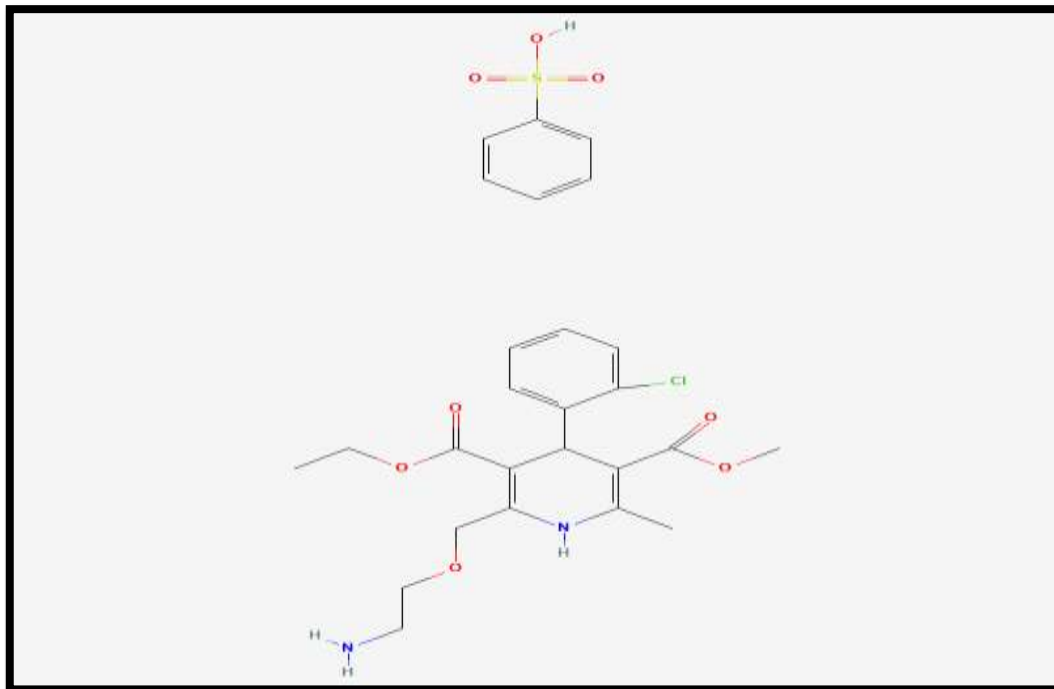
**Ahsan et al** According to a review paper by Ahsan et al. titled "Physicochemical properties and pharmacology of amlodipine besylate," amlodipine besylate (ADB) is a member of the dihydropyridine family and is well-known for being a successful first treatment for hypertension and Angina. It is used in concurrent disorders and has a slow beginning of action with little adverse effects. The primary mode of action is obstructing the influx of calcium ions into the cardiac and vascular muscles. ADB has a molecular weight of 567.1 and a white, crystalline appearance. Its 6.9 mg is the same as 5 mg of free base amlodipine (AM). This study concentrates on all the fundamental elements of ADB, which was one of the first treatment plans for cardiovascular illnesses during the previous 20 years.

**Hassen Fares et al.** In the paper "Amlodipine in hypertension: a first-line agent with efficacy for improving blood pressure," written by Hassen Fares et al., it was noted that hypertension is a major risk factor for cardiovascular disease. Adequate blood pressure management is still not optimum, despite the overwhelming data supporting the positive effects of antihypertensive medication on morbidity and death. Numerous medication classes with various efficacious profiles have been developed as a result of research into the treatment of hypertension.  $\beta$ -blockers, diuretics, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers are some of these medications. Among the earliest classes of antihypertensives, calcium channel blockers comprise a diverse range of drugs. Strong evidence for the prevention of cardiovascular events has been obtained from extensive randomized controlled studies, and amlodipine exhibits good efficacy and safety. Amlodipine ought to be used as a first-choice medication for hypertension.

**Mohammed Ali et al.**, According to a research paper titled "Formulations of Amlodipine" by Mohammed Ali et al., amlodipine (AD) is a calcium channel blocker that is primarily used to treat angina and hypertension. Recent research, however, indicates that its effectiveness extends beyond the management of cardiovascular conditions because it also exhibits antioxidant activity and is crucial for the process of apoptosis. As a result, it is also used, either alone or in conjunction with other medications, to treat conditions such as cerebrovascular stroke, neurodegenerative illnesses, leukemia, breast cancer, and so on. Since AD is a photosensitive medication, light protection is necessary. Many workers have attempted to create different AD dosage forms, both standard and non conventional .. All of the formulations—including fast-dissolving tablets, floating tablets, layered tablets, single-pill combinations, capsules, oral and transdermal films, suspensions, emulsions, mucoadhesive microspheres, gels, transdermal patches, and liposomal formulations—that have been developed to achieve maximum stability with the desired therapeutic action for the delivery of AD are highlighted in this review.

## STRUCTURE

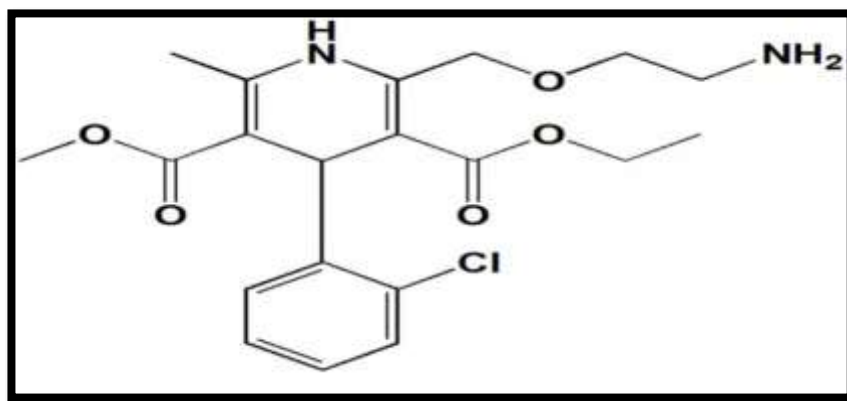
- Molecular formula -  $C_{26}H_{31}ClN_2O_8S$
- IUPAC name - benzenesulfonic acid;3-*O*-ethyl 5-*O*-methyl 2-(2-aminoethoxymethyl)-4- (2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate



## STRUCTURE ACTIVITY RELATIONSHIP (SAR)

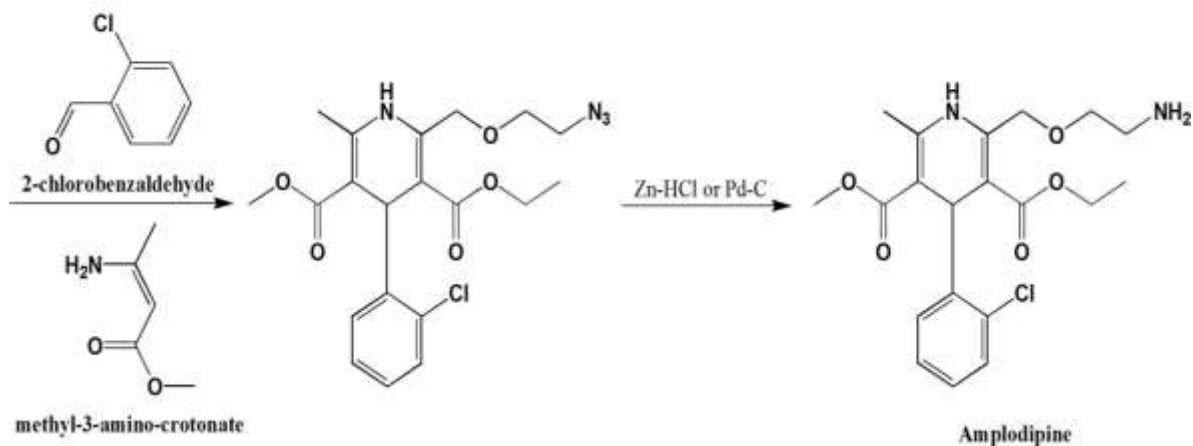
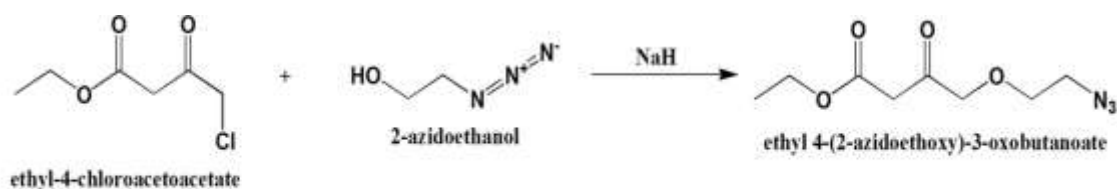
Dihydropyridines' calcium channel blockers' general structural activity can be summed up as follows:

1. R1 ought to be left unsubstituted.
2. R1 ought to be a readily separated group.
3. The addition of a basic amino ethyl ether chain at position R2 boosts the drug's effectiveness, whereas the presence of a H/aryl group reduces its activity.
4. The highest activity is obtained when an alkoxy carbonyl group is substituted for R3 and R5.
5. The activity is reduced when the ester group's alkyl chain is broken.
6. needs to be a phenyl ring.
7. S-enantiomers are more active than R-enantiomers.



## SYNTHESIS OF AMLODIPINE

1. In the presence of sodium hydride, ethyl-4-chloroacetoacetate combines with 3-azidoethanol to form ethyl-4-(2-azidoethoxy)-acetoacetate.
2. The final one reacts with methyl and 2-chlorobenzaldehyde-ethyl 3-aminocrotonate is produced. - 5-methyl-2- [methyl (-azido ethoxy)]4,4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridine carboxylate.
3. Amlodipine is produced when the aforementioned chemical is reduced.



## CLINICAL PHAMACOLOGY

### MECHANISM OF ACTION :

Amlodipine is a dihydropyridine calcium antagonist, also known as a calcium ion antagonist or slow-channel blocker, which prevents calcium ions from entering cardiac and vascular smooth muscle across the membrane. Amlodipine appears to bind to both dihydropyridine and non-dihydropyridine binding sites, according to experimental evidence. Extracellular calcium ions must enter cardiac muscle and vascular smooth muscle cells through certain ion channels in order for their contractile functions to function. Amlodipine selectively inhibits the inflow of calcium ions across cell membranes, primarily affecting smooth muscle cells in the vascular system as opposed to cardiac muscle cells.

Although negative inotropic effects have been observed in vitro, intact animals have not shown signs of these effects at therapeutic levels. The concentration of serum calcium remains unaffected by amlodipine.

Amlodipine is an ionised compound with a beginning of action that is gradual due to its gradual rate of association and dissociation with the receptor binding site. This substance is recognised as having an ionised state within the physiologic pH range ( $pK_a=8.6$ ). Amlodipine is a peripheral artery vasodilator that lowers blood pressure and peripheral vascular resistance by directly acting on vascular smooth muscle. Although the exact mechanisms by which amlodipine reduces angina are not entirely understood, the following are believed to be involved:

**Exertional Angina:** Amlodipine decreases the rate pressure product, which lowers the myocardial oxygen demand at any given exercise level, as well as the total peripheral resistance (afterload) that the heart must beat in order to sustain the patient.

**Vasospastic Angina:** In vitro studies on human coronary vessels and experimental animal models, amlodipine has been shown to inhibit constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium, adrenaline, serotonin, and thromboxane A<sub>2</sub> analogue. Amlodipine works well for vasospastic angina (Prinz metals or variation) because it inhibits coronary spasm.

#### PHARMACOKINETICS AND METABOLISM

Peak plasma concentrations of amlodipine are produced between 6 and 12 hours following oral administration of therapeutic dosages. It has been calculated that absolute bioavailability ranges from 64 to 90%. Food has no effect on the bioavailability of amlodipine. Through hepatic metabolism, amlodipine is substantially (approximately 90%) transformed to inactive metabolites; 10% of the parent substance and 60% of the metabolites are eliminated in the urine. Ex vivo investigations have revealed that in hypertension individuals, 93% of the medication in circulation is linked to plasma proteins. With a terminal elimination half-life of roughly 30 to 50 hours (roughly two days), removal from plasma is biphasic. After 7–8 days of consecutive daily administration, amlodipine reaches steady-state plasma levels.

Renal impairment does not significantly affect the pharmacokinetics of amlodipine. Therefore, the initial dose may be given as usual to patients with renal insufficiency. A lower starting dose may be necessary for elderly and hepatic insufficiency patients due to their slower clearance of amlodipine, which causes a rise in AUC of roughly 40–60%. A comparable rise in AUC was noted in individuals suffering from moderate to severe heart failure.

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#### PHARMACODYNAMICS

##### *Hemodynamics:*

Patients with moderate hypertension (diastolic pressure 90 to 104 mmHg) showed a reaction that was approximately 50% less than those with n (diastolic pressure 105 to 114 mmHg).

Blood pressure changes in normotensive patients were not clinically significant ( $+1/-2$  mmHg). Therapeutic doses of amlodipine decreased renal vascular resistance, increased glomerular filtration rate, and improved effective renal plasma flow in hypertensive patients with normal renal function, all without affecting the filtration fraction or proteinuria. Similar to other hemodynamics, amlodipine causes vasodilation after therapeutic amounts are administered to hypertensive patients, which lowers standing and supine blood pressure. With chronic dosage, there is no discernible change in heart rate or plasma catecholamine levels to go along with these blood pressure reductions. Chronic oral amlodipine administration in clinical trials did not result in clinically significant changes in heart rate or blood pressure in normotensive patients with angina, despite the fact that acute intravenous administration of the medication lowers arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina. When chronically administered orally once day, the antihypertensive impact lasts for a minimum of twenty-four 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 the height of pretreatment elevation; 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). Therapeutic doses of amlodipine decreased renal vascular resistance, increased glomerular filtration rate, and improved effective renal plasma flow in hypertensive patients with normal renal function, all without affecting the filtration fraction or proteinuria. Similar to other calcium channel blockers, amlodipine-treated patients with normal ventricular function have, on hemodynamic measurements of cardiac function at rest and during exercise (or pacing), typically shown a slight increase in cardiac index without a discernible effect on  $dP/dt$  or left ventricular end diastolic pressure (r volume)

When given in the therapeutic dose range to healthy humans and animals, including when co-administered with beta-blockers in humans, hemodynamic studies have not shown that amlodipine has a detrimental inotropic effect. However, similar results have been seen with medications having notable adverse inotropic effects in normal or well-compensated heart failure patients.

**Electrophysiologic Effects:** In humans or intact animals, amlodipine has no effect on atrioventricular conduction or sinoatrial nodal function. The intravenous treatment of 10 mg did not significantly modify the sinus node recovery time after pacing or the A-H and H-V conduction in patients with chronic stable angina. Patients using amlodipine and concurrent beta-blockers experienced similar outcomes. There were no negative effects on electrocardiographic measures in clinical trials where individuals with either hypertension or angina received amlodipine in addition to beta-blockers.

Amlodipine medication did not change electrocardiographic intervals or result in greater degrees of AV blocks in clinical trials including angina patients on its own.

A total of 15 double-blind, placebo-controlled, randomized trials with 800 patients on amlodipine and 538 on placebo have shown the antihypertensive efficacy of amlodipine. When administered once daily, patients with mild to moderate hypertension experienced statistically significant reductions in their blood pressure in both the supine and standing positions 24 hours after the dose, with an average of roughly 12/6 mmHg in the standing position and 13/7 mmHg in the supine position. Little variation was seen in the blood pressure effect's peak and trough throughout the course of the 24-hour dosing interval.

In patients followed for up to a year, tolerance was not shown. Within the advised dosage range, the three parallel, fixed dose, dose response experiments demonstrated that the drop in standing and supine blood pressure was dose-related. Both elderly and younger patients experienced comparable effects on diastolic pressure. Perhaps as a result of higher baseline systolic pressure, the effect on systolic pressure was stronger in older patients. The outcomes for White and Black patients were comparable. Young Patients: A total of 258 hypertensive patients between the ages of 6 and 17 were randomised to receive either 2.5 or 5 mg of amlodipine once daily for four weeks, followed by another four weeks at the same dose or a placebo.

Although it is challenging to evaluate, the treatment impact is most likely less than 5 mmHg systolic on the 5 mg dose. Adverse occurrences resembled those observed in adulthood.

**Effects in Chronic Stable Angina:** Eight placebo-controlled, double-blind clinical trials with a maximum duration of six weeks, involving 1038 patients (684 on amlodipine and 354 on placebo), assessed the efficacy of 5 to 10 mg/day of amlodipine in exercise-induced angina. The 10 mg dose was associated with significant increases in exercise time (on a bicycle or treadmill) in 5 out of 8 investigations. Exercise time was restricted by symptoms on average by 12.8% (63 seconds) for amlodipine 10 mg and 7.9% (38 seconds) for amlodipine 5 mg. In multiple investigations, amlodipine 10 mg also reduced the incidence of angina attacks and lengthened the duration to 1 mm ST segment deviation.

**Impact on Vasospastic Angina:** Amlodipine treatment reduced attacks by around 4/week in a 4-week double-blind, placebo-controlled clinical trial including 50 patients, as opposed to a placebo drop of about 1/week ( $p < 0.01$ ). The absence of clinical improvement caused 7 out of 27 placebo patients and 2 out of 23 amlodipine patients to stop the research.

Amlodipine Studies in Patients with Congestive Heart Failure

**Research on Congestive Heart Failure Patients:** Four 8–12 week studies including 697 patients with NYHA class II/III heart failure have compared amlodipine besylate to placebo. Based on metrics such as exercise tolerance, NYHA classification, symptoms, and left ventricular ejection fraction, there was no indication of worsening heart failure in these investigations.

In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study, amlodipine besylate 5 to 10 mg was found to have no effect on symptoms of heart failure or the combined endpoint of all-cause mortality and cardiac morbidity (defined as life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure) in 1153 patients with NYHA classes III (N=931) or IV (N=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors. Amlodipine besylate did not affect the NYHA classification, heart failure symptoms, or the combined endpoint of all-cause mortality and cardiac morbidity (defined by acute myocardial infarction, hospitalization for worsening heart failure, or life-threatening arrhythmia). For individuals on amlodipine besylate, the total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) and 246/583 (42%) for patients on placebo; the cardiac morbid events accounted for approximately 25% of the study's endpoint.

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## CLINICAL USES

### 1. Hypertension

Tablets containing amlodipine besylate are prescribed to treat hypertension. They can be taken either by alone or in addition to other antihypertensive medications.

Reducing hypertension shields against heart attacks, strokes, and kidney issues.

### 2. Cardiac Arteriosclerosis (CAD):

The symptomatic treatment of chronic stable angina is indicated by the use of Amlodipine Besylate Tablets.

Amlodipine Besylate Tablets are recommended for the treatment of proven or suspected cases of vasospastic angina (also known as Prinzmetal's or Variant Angina). Tablets containing amlodipine besylate can be used alone or in conjunction with other antianginal medications.

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## INDICATIONS AND USAGE

**Hypertension:** The medication Amlodipine Besylate Tablets is prescribed to treat hypertension. They can be used both on their own and in conjunction with other antihypertensive medications.

**Coronary Artery Disease (CAD)**

Amlodipine Besylate Tablets are recommended for the symptomatic treatment of chronic stable angina in patients with coronary artery disease (CAD). Amlodipine Besylate Tablets can be taken either on their own or in conjunction with other antianginal medications.

Treatment for confirmed or suspected cases of vasospastic angina (also known as Prinzmetal's or Variant Angina) involves the use of Amlodipine Besylate Tablets. The Amlodipine Besylate Tablets can be taken either by itself or in conjunction with other antianginal medications.

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## CONTRAINDICATIONS

Amlodipine Besylate Tablets should not be administered to anyone who have a history of amlodipine sensitivity.

It has proven to reduce BP variability and successfully lower BP. Amlodipine also controls BP in patients with a systolic/diastolic BP of 130/80 mm Hg or higher, diabetes, or chronic kidney disease without worsening glycemic or kidney function. Additionally, amlodipine is a wise choice for older adults due to its ability to control BP and protect against stroke and myocardial infarction. Side effects of amlodipine include edema, palpitations, dizziness, and flushing, which are more common with the higher dose of 10 mg. Amlodipine is cost effective and predicted to be cost saving when compared with usual care.

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