MONOGRAPH FOR HEALTH PROFESSIONALS

AMLODIPINE BESYLATE TABLETS USP
5 mg and 10 mg

PRESCRIPTION ONLY MEDICATION

Antihypertensive-Antianginal Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	Tablet /5 mg & 10 mg	Lactose B.P. 200 Mesh, Magnesium Stearate, Starch Maize B.P., Sodium Starch Glycolate, Collodial Anhydrous Silica, and Talc Purified.

INDICATIONS AND CLINICAL USE

Hypertension

Amlodipine besylate is indicated in the treatment of mild to moderate essential hypertension.

Combination of amlodipine besylate with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.

Chronic Stable Angina

Amlodipine besylate is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.

Amlodipine besylate may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

Geriatrics (≥ 65 years of age)
Evidence from clinical studies suggests that use in the geriatric population is associated with differences in safety and exposure (see WARNINGS AND PRECAUTIONS; PHARMACOLOGICAL INFORMATION; and DOSAGE AND METHOD OF USE).

Pediatrics (6 – 17 years of age)
Amlodipine efficacy has been shown in a clinical trial for the treatment of hypertension in pediatric patients aged 6 – 17 years. Dosing and safety considerations are to be taken into

account when prescribing pms-AMLODIPINE in this patient population (see WARNINGS AND PRECAUTIONS; PHARMACOLOGICAL INFORMATION; and DOSAGE AND METHOD OF USE).

The use of Amlodipine besylate in children less than 6 years of age is not recommended (see WARNINGS AND PRECAUTIONS - Special Populations).

CONTRAINDICATIONS

Amlodipine besylate is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines* and in patients with severe hypotension (less than 90 mmHg systolic).

*Amlodipine besylate is a dihydropyridine calcium channel blocker.

Amlodipine is transferred into human breast milk, therefore amlodipine besylate is contraindicated during breast-feeding (see WARNINGS AND PRECAUTIONS).

Amlodipine besylate is also contraindicated in patients with:

- severe hypotension
- shock including cardiogenic shock
- obstruction of the outflow tract of the left ventricle (e.g., high-grade aortic stenosis)
- hemodynamically unstable heart failure after acute myocardial infarction

WARNINGS AND PRECAUTIONS

General

Beta-blocker Withdrawal
Amlodipine besylate gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta- blocker.

Cardiovascular

Increased Angina and/or Myocardial Infarction
Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Use in Patients with Congestive Heart Failure
Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that amlodipine besylate had no overall deleterious effect on

survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.

Of note, in an amlodipine long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV), the reported incidence of pulmonary edema was higher in the amlodipine-treated group than in the placebo group. Calcium channel blockers, including amlodipine, may increase the risk of future cardiovascular events and mortality.

Hypotension
Amlodipine besylate may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Peripheral Edema
Mild to moderate peripheral edema was the most common adverse event in the clinical trials (see ADVERSE REACTIONS). The incidence of peripheral edema was dose- dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Hepatic/Biliary/Pancreatic

Use in Patients with Impaired Hepatic Function
There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged (see PHARMACOLOGICAL INFORMATION, Pharmacokinetics). Amlodipine besylate should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see DOSAGE AND METHOD OF USE).

Patients with Severe Hepatic Impairment or Hepatic Failure
Because amlodipine besylate is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, it should be administered cautiously and at reduced dosages in patients with severely impaired hepatic function (see DOSAGE AND METHOD OF USE, Recommended Dose and Dosage Adjustment). Slow dose titration and careful monitoring are required in patients with severe hepatic impairment.

Concomitant Use with Strong Inhibitors of CYP 3A4
Use of Amlodipine besylatewith drugs that result in strong inhibition of CYP 3A4, such as ketoconazole, clarithromycin, ritonavir, may lead to increased plasma levels of amlodipine and associated serious events (see DRUG INTERACTIONS). Such concomitant use should be avoided.
An observational study demonstrated an increased risk of hospitalization with acute kidney injury when amlodipine was used concomitantly with clarithromycin in elderly patients (> 65

years of age) compared to when it was used concomitantly with azithromycin, odds ratio [amlodipine: 1.61 (95% C.I. 1.29 – 2.02)].

Sexual Health
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Reversible adverse effects on male rat fertility have also been suggested (see TOXICOLOGY, Reproduction and Teratology).

USE IN SPECIAL POPULATIONS

Pregnant Women
There is no clinical experience with amlodipine besylate in pregnant women.
Amlodipine besylate should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Although amlodipine was not teratogenic in the rat and rabbit, some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There was no effect on the fertility of rats treated with amlodipine.

Nursing Women
In human study, the mean maternal daily dose of amlodipine was 6.0 mg and the medians of the plasma and milk concentrations of amlodipine were 15.5 and 11.5 ng/mL, respectively, with median milk/plasma concentration ratio of 0.85. Since amlodipine safety in newborns has not been established, Amlodipine besylate should not be given to nursing mothers. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see CONTRAINDICATIONS).

Pediatrics (0 – 17 years of age)
The use of amlodipine besylate is not recommended in patients less than 6 years of age since safety and efficacy have not been established in that population.

In pediatric patients aged 6 – 17 years, safety and efficacy studies beyond 8 weeks of duration, for the treatment of hypertension, have not been conducted. The prescription in this population should be based on a careful risk/benefit assessment of the limited available information. The risk/benefit assessment should be conducted by a qualified physician.

Geriatrics (≥ 65 years of age)
In elderly patients (≥ 65 years) clearance of amlodipine is decreased with a resulting increase in AUC (see PHARMACOLOGICAL INFORMATION, Pharmacokinetics). In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (< 65 years). Adverse reactions include edema, muscle cramps and dizziness. Amlodipine besylate should be used cautiously in elderly patients. Dosage adjustment is advisable (see DOSAGE AND METHOD OF USE).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Amlodipine besylate has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs. placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild to moderate severity.

Hypertension
In the 805 hypertensive patients treated with amlodipine besylate in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: oedema (8.9%), and headache (8.3%).

The following adverse reactions were reported with an incidence of ≥ 0.5% in the controlled clinical trials program (n = 805):

Cardiovascular: oedema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%).
Skin and Appendages: pruritus (0.7%).
Musculoskeletal: muscle cramps (0.5%).
Central and Peripheral Nervous System: headaches (8.3%), dizziness (3.0%), paraesthesia (0.5%).
Autonomic Nervous System: flushing (3.1%), hyperhidrosis (0.9%), dry mouth (0.7%).
Psychiatric: somnolence (1.4%).
Gastrointestinal: nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%).
General: fatigue (4.1%), pain (0.5%).

Angina
In the controlled clinical trials in 909 angina patients treated with amlodipine besylate, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: oedema (9.9%) and headache (7.8%).

The following adverse reactions occurred at an incidence of ≥ 0.5% in the controlled clinical trials program (n = 909);

Cardiovascular: oedema (9.9%), palpitations (2.0%), postural dizziness (0.6%).
Skin and Appendages: rash (1.0%), pruritus (0.8%).
Musculoskeletal: muscle cramps (1.0%).

Central and Peripheral Nervous System: headaches (7.8%), dizziness (4.5%), paraesthesia (1.0%), hypoesthesia (0.9%).
Autonomic Nervous System: flushing (1.9%).
Psychiatric: somnolence (1.2%), insomnia (0.9%), nervousness (0.7%).
Gastrointestinal: nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%).
Respiratory System: dyspnoea (1.1%).
Special Senses: visual impairment (1.3%), tinnitus (0.6%).
General: fatigue (4.8%), pain (1.0%), asthenia (1.0%).

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Amlodipine besylate has been evaluated for safety in about 11,000 patients with hypertension and angina. The following events occurred in < 1% but > 0.1% of patients in comparative clinical trials (double-blind comparative vs. placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, myocardial infarction, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis, chest pain.
Central and Peripheral Nervous System: hypoesthesia/paraesthesia, neuropathy peripheral, tremor, vertigo.
Gastrointestinal: anorexia, constipation, dysphagia, vomiting, gingival hyperplasia, change in bowel habits, dyspepsia.
General: allergic reaction, asthenia[+], back pain, pain, hot flushes, malaise, rigors, and weight increased/weight decreased.
Musculoskeletal System: arthralgia, arthrosis, myalgia, muscle cramps.
Psychiatric: sexual dysfunction (male[+] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood altered.
Respiratory System: dyspnoea, epistaxis.
Skin and Appendages: pruritus, rash erythematous, rash maculopapular, erythema multiforme.
Special Senses: conjunctivitis, diplopia, eye pain, visual impairment, tinnitus.
Urinary System: pollakiuria, micturition disorder, nocturia.
Autonomic Nervous System: dry mouth, hyperhidrosis.
Metabolic and Nutritional: hyperglycaemia, thirst.
Hemopoietic: leukopenia, purpura, thrombocytopenia.
Reproductive System and Breast Disorders: gynecomastia, erectile dysfunction.
[+]These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in ≤ 0.1% of patients: cardiac failure, skin discoloration*, urticaria*, skin dryness, Stevens-Johnson syndrome, alopecia*, twitching, ataxia, hypertonia*, migraine, apathy, amnesia, gastritis*, pancreatitis*, increased appetite, coughing*, rhinitis*, parosmia, taste perversion*, and xerophthalmia.
*these events were observed in marketing experience as well.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty.

Post-Market Adverse Drug Reactions

In post-marketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Post-marketing reporting has also revealed cases of extrapyramidal disorders induced by amlodipine.

DRUG INTERACTIONS

Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Co-administration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.

Drug-Drug Interactions

Table 1: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Drugs known to be inhibitors of the cytochrome P450 system (diltiazem, azole antifungals, erythromycin, quinidine, terfenadine and warfarin)	CTT	Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers (18 to 43 years of age) increased the systemic exposure of amlodipine by 22%.	These pharmacokinetic changes may be more pronounced in the elderly. Close monitoring and dose adjustment may be required.

Proper name	Ref	Effect	Clinical comment
Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)	T	May significantly increase the plasma concentrations of amlodipine to a greater extent than diltiazem.	Amlodipine should be used with caution together with CYP3A4 inhibitors and monitoring of therapy is required. Appropriate dosage adjustment of amlodipine may be necessary when used with CYP3A4 inhibitors. Patients should be advised to seek medical attention if they experience edema or swelling of the lower extremities; sudden, unexplained weight gain; difficulty breathing; chest pain or tightness; or hypotension as indicated by dizziness, fainting, or orthostasis. Avoid concomitant administration of amlodipine with strong CYP3A4 inhibitors.
Clarithromycin	CT	In elderly patients (> 65 years of age), concomitant use of amlodipine with clarithromycin was associated with increased risk of hospitalization with acute kidney injury.	Avoid concomitant use.
Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin	T	There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine which in turn can result in decreased blood pressure lowering effects.	Amlodipine should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Hence, monitoring of therapy is required**.**
Drugs known to be biotransformed via P450 (benzodiazepines, flecainide, imipramine, propafenone, theophylline)	T	Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.	
Cimetidine, warfarin, digoxin	CT	Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated that cimetidine did not alter the pharmacokinetics of amlodipine and that amlodipine did not change warfarin-induced prothrombin response time nor did it change serum digoxin levels or digoxin renal clearance in normal volunteers.	
Antacids	CT	Concomitant administration of magnesium hydroxide and aluminum hydroxide had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.	

Proper name	Ref	Effect	Clinical comment
Beta-blockers	T	Blood pressure lowering effect of beta-blockers may be increased by amlodipine.	When beta-adrenergic receptor blocking drugs are administered concomitantly with amlodipine besylate, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.
Sildenafil	CT	A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on AUC or C_{max} of amlodipine. When sildenafil (100 mg) was co-administered with amlodipine, 5 or 10 mg in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.	
Atorvastatin	CT	In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine besylate with 80 mg of atorvastatin resulted in no clinical significant change in the AUC (average of 18% increase) or C_{max} or T_{max} of atorvastatin.	Close monitoring is required.
Simvastatin	CT	Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone.	Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
Cyclosporin	CT	No drug interaction studies have been conducted with cyclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients. A prospective study in hypertensive renal transplant patients (N = 11) showed on an average of 40% increase in trough cyclosporin levels when concomitantly treated with amlodipine.	Consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.
Tacrolimus	C	There is a risk of increased tacrolimus blood levels when co-administered with amlodipine.	In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustments of tacrolimus when appropriate.

Proper name	Ref	Effect	Clinical comment
Mechanistic Target of Rapamycin (mTOR) Inhibitors	CT T	mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.	
Dantrolene	T	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene.	Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Legend: CT = Clinical Trial; T = Theoretical; C = Case Study

Drug-Food Interactions

Interaction with Grapefruit Juice

Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects (See PHARMACOLOGICAL INFORMATION, Pharmacokinetics). Hence, monitoring of therapy is required.

Drug-Herb Interactions

St. John's Wort is an inducer of CYP3A4. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine which in turn can result in decreased blood pressure lowering effects. Amlodipine should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Hence, monitoring of therapy is required.

DOSAGE AND METHOD OF USE

Dosing Considerations

Dosage should be individualized depending on patient's tolerance and responsiveness.

Recommended Dose and Dosage Adjustment

For both hypertension and angina, the recommended initial dose of Amlodipine besylate is 5 mg once daily. If necessary, dose can be increased after 1 – 2 weeks to a maximum dose of 10 mg once daily.

Use in the Elderly or in Patients with Impaired Renal Function
The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see WARNINGS AND PRECAUTIONS).

Use in Patients with Impaired Hepatic Function
Dosage requirements have not been established in patients with impaired hepatic function. When Amlodipine besylate is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see WARNINGS AND PRECAUTIONS).

Use in Pediatric Patients (6 – 17 years of age)
The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied; dose should be determined based upon the medical need of the patients (See PHARMACOLOGICAL INFORMATION).

OVERDOSAGE

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of amlodipine besylate is limited. Gastric lavage may be worthwhile in some cases. In healthy volunteers, the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As amlodipine besylate is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects

of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

PHARMACOLOGICAL INFORMATION

Mechanism of Action

Amlodipine besylate is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of these tissues 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. Within the physiologic pH range, amlodipine is an ionized compound and its kinetic interaction with the calcium channel receptor is characterized by the gradual association and dissociation with the receptor binding site. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites.

A. **Hypertension:** The mechanism by which amlodipine reduces arterial blood pressure involves direct peripheral arterial vasodilation and reduction in peripheral vascular resistance.

B. **Angina:** The precise mechanism by which amlodipine relieves angina has not been fully delineated. Amlodipine is a dilator of peripheral arteries and arterioles which reduces the total peripheral resistance and, therefore, reduces the workload of the heart (afterload). The unloading of the heart is thought to decrease ischemia and relieve effort angina by reducing myocardial energy oxygen consumption and oxygen requirements.

Pharmacodynamics

Hemodynamics
Following administration of recommended 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 any significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily oral administration (5 and 10 mg once daily), antihypertensive effectiveness is maintained throughout the 24 hours dose interval with minimal peak to trough differences in plasma concentration. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been

reported after oral administration of amlodipine. In normotensive patients with angina amlodipine has not been associated with any clinically significant reductions in blood pressure or changes in heart rate.

Negative inotropic effects have not been observed when amlodipine was administered at the recommended doses to man, but has been demonstrated in animal models. Hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in angina patients with normal ventricular function have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction.

Electrophysiologic Effects
Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals, or man. In patients with chronic stable angina, intravenous administration of 10 mg of amlodipine and a further 10 mg of amlodipine after a 30 min. interval produced peripheral vasodilation and afterload reduction, but did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients, amlodipine as monotherapy did not alter electrocardiographic intervals.

Effects in Hypertension
Pediatric Patients
Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine besylate 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

Pediatric safety and efficacy studies beyond 8 weeks of duration have not been conducted. In addition, the long-term effect of amlodipine on growth and development, myocardial growth and vascular smooth muscles has not been studied.

Pharmacokinetics

Absorption
After oral administration of therapeutic doses of amlodipine, absorption occurs gradually with peak plasma concentration reached between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Metabolism
Amlodipine is metabolized through the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. 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. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Excretion
Elimination from the plasma is biphasic with a terminal elimination half-life of about 35 – 50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Special Populations and Conditions

Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine, geometric mean C_{max} of amlodipine was 6.2 ng/mL when the drug was administered with grapefruit juice and 5.8 ng/mL when administered with water. Mean T_{max} of amlodipine was 7.6 hours with grapefruit juice and 7.9 hours with water. Geometric mean $AUC_{0-\infty}$ was 315 ng/hr/mL with grapefruit juice and 293 ng/hr/mL with water. Geometric mean bioavailability of amlodipine was 85% when administered with grapefruit juice and 81% when administered with water.

Pediatrics
Two studies were conducted to evaluate the use of amlodipine besylate in a pediatric population.

In one study (pharmacokinetic), sixty-two hypertensive patients aged greater than 6 years received doses of amlodipine besylate between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults (see DOSAGE AND METHOD OF USE). The mean absorption rate constant (K_a) in children (0.85 hr^{-1}) is approximately 50% higher than that in healthy adults (0.55 hr^{-1}, range of 0.28 – 1.09 hr^{-1}).

Gender Effect
In a second trial (clinical), a pattern of greater reductions in both systolic and diastolic blood pressure in females than in males was observed. Mean change in systolic blood pressure from baseline to end of study: amlodipine 2.5 mg: males, -6.9 mmHg (n = 51); females, -8.9 mmHg (n = 32); amlodipine 5.0 mg: males, -6.6 mmHg (n = 63); females, -14.0 mmHg (n = 23); placebo males, -2.5 mmHg (n = 54), females, -3.8 mmHg (n = 33).

Renal Insufficiency
The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Plasma concentrations in the patients with moderate to severe renal failure were higher than in the normal subjects. Accumulation and mean elimination half-life in all patients were within the range of those observed in other pharmacokinetic studies with amlodipine in normal subjects.

Geriatrics
In elderly hypertensive patients (mean age 69 years) there was a decrease in clearance of amlodipine from plasma as compared to young volunteers (mean age 36 years) with a resulting increase in the area under the curve (AUC) of about 60%.

Hepatic Insufficiency
Following single oral administration of 5 mg of amlodipine, patients with chronic mild-moderate hepatic insufficiency showed about 40% increase in AUC of amlodipine as compared to normal volunteers. This was presumably due to a reduction in clearance of amlodipine as the terminal elimination half-life was prolonged from 34 hrs in young normal subjects to 56 hrs in the elderly patients with hepatic insufficiency.

Patients with Severe Hepatic Impairment or Hepatic Failure:
Because amlodipine besylate is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, it should be administered cautiously and at reduced dosages in patients with severely impaired hepatic function (see DOSAGE AND METHOD OF USE, Recommended Dose and Dosage Adjustment). Slow dose titration and careful monitoring are required in patients with severe hepatic impairment.

STORAGE TEMPERATURE

Do not store above 30ºC. Protect from light.

CONTENTS, COMPOSITION, PACKAGING AND EXCIPIENTS STATEMENT

Tablets

5 mg: Each small, white, biconvex tablet with a diameter of 6 mm contains 5 mg of amlodipine, as amlodipine besylate USP, and the following non-medicinal ingredients: Lactose B.P. 200 Mesh, Magnesium Stearate, Starch Maize B.P., Sodium Starch Glycolate, Collodial Anhydrous Silicia and Talc Purified. Available in bottles of 100 and 1000 tablets.

10 mg: Each small, white, biconvex tablet with a diameter of 8 mm contains 10 mg of amlodipine, as amlodipine besylate USP, and the following non-medicinal ingredients: Lactose B.P. 200 Mesh, Magnesium Stearate, Starch Maize B.P., Sodium Starch Glycolate, Collodial Anhydrous Silicia and Talc Purified. Available in bottles of 100 and 1000 tablets.

CLINICAL INFORMATION

Several trials have evaluated the antihypertensive efficacy of amlodipine as monotherapy versus other agents like angiotensin receptor blockers (ARBs), diuretics and ACE inhibitors (ACEIs). Data from these trials suggest that amlodipine has good efficacy and safety as a first-line antihypertensive agent, not only for controlling BP, but also for safely improving patient outcomes, and these trials will be discussed below. The efficacy of amlodipine as an antihypertensive has been demonstrated by multiple double-blinded, placebo-controlled, randomised studies. These studies demonstrated that once-daily administration of amlodipine in patients with mild to moderate hypertension leads to statistically significant placebo-corrected reductions averaging about 13/7 mmHg in supine and 12/6 mmHg standing blood pressures, 24 hours post-dose. In addition, maintenance of blood pressure control over the 24-hour dosing interval was observed, with little difference in peak and trough effect. No tolerance to amlodipine occurred in patients studied for up to 1 year. Young and older patients showed similar effects on diastolic pressure, while the effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Coronary artery disease (CAD) was detected angiographically in 1991 patients. They were enrolled in the randomized trial, 'Comparison of Amlodipine versus Enalapril to Limit Occurrence of Thrombosis (CAMELOT), and was given either amlodipine (10 mg), enalapril (20 mg), or placebo, and was followed for over 2 years. To begin with, the baseline BP was low, with an average of 129/78. However, both amlodipine and enalapril groups showed similar lowering of BP, 4.8/2.5 and 4.9/2.4, respectively. A lower rate of cardiovascular events (primary outcome) occurred in patients on amlodipine as compared to those on enalapril or placebo (Figure 1). The study also showed that the normotensive patients (number treated =16) that were treated with amlodipine, had a decline in cardiovascular events, showed evidence of regression of atherosclerotic changes, had fewer hospitalizations, and had a significant decrease of non-fatal myocardial infarction by 26 % and stroke or transient ischaemic attack by 50 % (Figure 2).

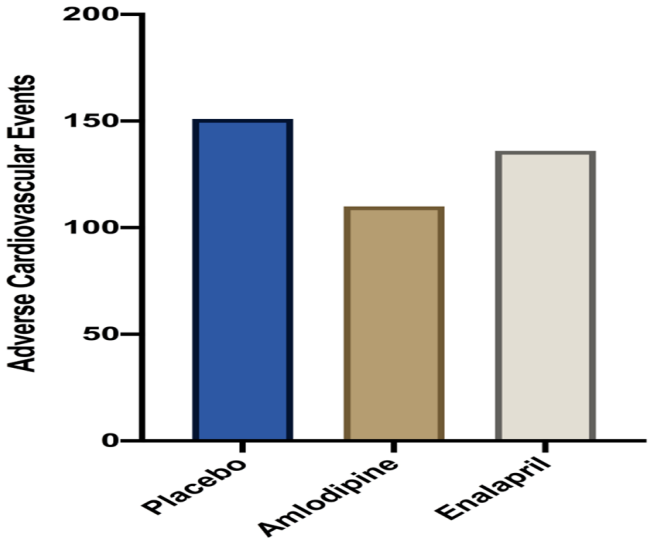


Figure 1: Comparison of primary end point outcomes of adverse cardiovascular (CV) events between the three study arms. CV events were seen in 151 (23.1%) patients in the placebo group, 110 (16.6%) in the amlodipine group and 136 (20.2 %) in the Enalapril group

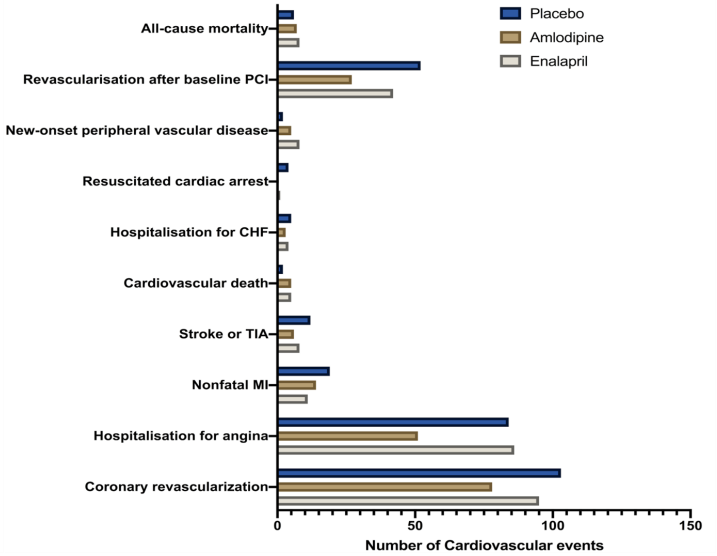


Figure 2: A comparison of individual components and secondary outcomes of the cardiovascular events in the three study arms. The coronary revascularization component was reduced the most in the amlodipine group (N=78), as compared to enalapril (N=95) and placebo (N=103). Hospitalization for angina was similarly reduced in the amlodipine group (N=51), as compared to enalapril (N=86) and placebo (N=84). The rate of revascularization after baseline PCI was significantly reduced in the amlodipine arm (N=27), as compared to the enalapril arm (N=42) and placebo (N=52).

The ALLHAT (Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial) which enrolled over 33000 patients with HTN and one CHD risk factor, was one of the largest ever randomised trials of antihypertensive drugs. The objective of the ALLHAT trial was to determine if the incidence of CHD or other CV diseases is lower in patients treated with a diuretic, a CCB, or an ACEI. Patients were randomised to Lisonopril, Chlorthalidone, or Amlodipne with a mean follow-up of about 4.9 years6. The primary outcome was considered to be a combined fatal CHD or nonfatal myocardial infarct, analysed by intent-to-treat. Combined CHD including primary outcomes, coronary vascularization or angina with hospitalisation, and combined CVD which included combined CHD, stroke, treated angina without hospitalisation, heart failure (HF), and peripheral vascular disease, and all-cause mortality and stroke as such, were all taken as secondary outcomes. The primary and secondary outcomes for all-cause mortality were almost similar among the various groups. The trial demonstrated that amlodipine can be recommended as a first-line agent in the treatment of HTN since it was neither superior nor inferior as compared to ACEIs or thiazide diuretics in managing HTN in patients with other comorbid conditions (Figure 3(a) and (b)).

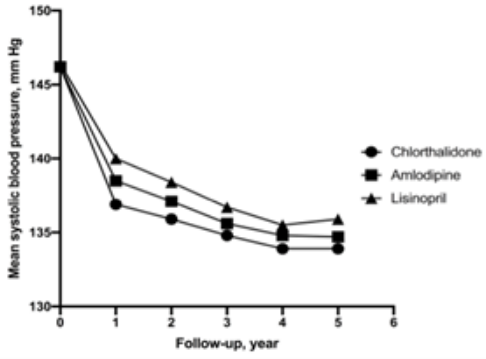


Figure 3a: Mean Systolic by year during follow-up in the 3 treatment arms of the ALLAHAT Study.

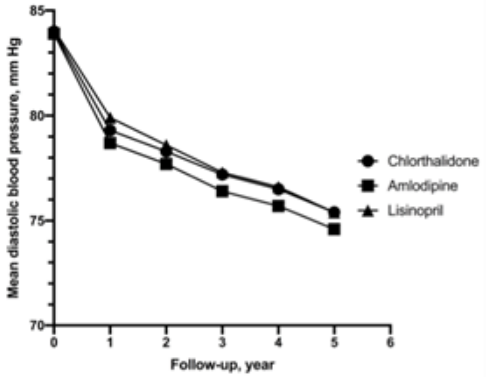


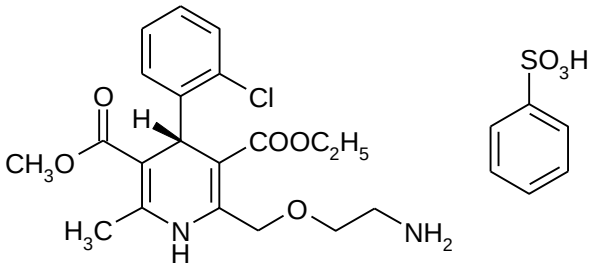
Figure 3b: Diastolic Blood Pressure by year during follow-up in the 3 treatment arms of the ALLAHAT Study.

PHARMACEUTICAL DRUG INFORMATION
Drug Substance

Drug Substance

Proper Name:	Amlodipine Besylate
Chemical Name:	3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulfonate
Molecular formula:	$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$
Molecular mass:	567.1 g/mol

Structural formula:



enantiomer

Physicochemical properties:

Description:	Amlodipine is a white or almost white powder.
Solubility:	Amlodipine is slightly soluble in water, freely soluble in methanol, and sparingly soluble in ethanol.
Melting Point:	The melting range is 201ºC to 205ºC with decomposition.

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