PRODUCT MONOGRAPH

[Pr] pharma-AMLODIPINE

Amlodipine besylate tablets USP
2.5 mg, 5 mg and 10 mg

Antihypertensive-Antianginal Agent

PHARMASCIENCE INC.
6111 Av. Royalmount, suite 100
Montréal, Québec
H4P 2T4

www.pharmascience.com

Date of Revision:
January 5, 2021

Submission Control No.: 247255

Table of Contents

[Pr] pharma-AMLODIPINE

Amlodipine Besylate Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet / 2.5 mg, 5 mg, 10 mg	Magnesium stearate, microcrystalline cellulose, sodium starch glycolate and trisodium citrate.

INDICATIONS AND CLINICAL USE

Hypertension

pharma-AMLODIPINE (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

pharma-AMLODIPINE 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.

pharma-AMLODIPINE 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; ACTION AND CLINICAL PHARMACOLOGY; and DOSAGE AND ADMINISTRATION).

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 pharma-AMLODIPINE in this patient population (see WARNINGS AND PRECAUTIONS; ACTION AND CLINICAL PHARMACOLOGY; and DOSAGE AND ADMINISTRATION).

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

CONTRAINDICATIONS

pharma-AMLODIPINE 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 pharma-AMLODIPINE is contraindicated during breast-feeding (see WARNINGS AND PRECAUTIONS).

pharma-AMLODIPINE 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)
- haemodynamically unstable heart failure after acute myocardial infarction

WARNINGS AND PRECAUTIONS

General

Beta-blocker Withdrawal
pharma-AMLODIPINE 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
pharma-AMLODIPINE 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 ACTION AND CLINICAL PHARMACOLOGY, 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 ADMINISTRATION).

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 ADMINISTRATION, 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 besylate with 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).

Special Populations

Pregnant Women: There is no clinical experience with amlodipine besylate in pregnant women. pharma-AMLODIPINE 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, pharma-AMLODIPINE 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 ACTION AND CLINICAL PHARMACOLOGY, 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. pharma-AMLODIPINE should be used cautiously in elderly patients. Dosage adjustment is advisable (see DOSAGE AND ADMINISTRATION).

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 l,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%), hypoaesthesia (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: hypoaesthesia/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 $\leq 0.1\%$ 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. Coadministration 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)	CT T	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.
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,	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	

Proper name	Ref	Effect	Clinical Comment
theophylline)		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.	
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 Cmax 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 mm Hg systolic and 7 mm Hg diastolic.	
Atorvastatin	CT	In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine besylate with 80 mg of atorvastatin resulted in no significant change in the AUC (average of 18% increase) or Cmax or Tmax 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	Consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.

Proper name	Ref	Effect	Clinical Comment
		of 40% increase in trough cyclosporin levels when concomitantly treated with 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.
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 ACTION AND CLINICAL PHARMACOLOGY, 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 ADMINISTRATION

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 pharma-AMLODIPINE 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 patients' 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 ACTION AND CLINICAL PHARMACOLOGY).

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

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

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.

ACTION AND CLINICAL PHARMACOLOGY

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 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 Cmax 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 Tmax 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 in a pediatric population.

In one study (pharmacokinetic), sixty-two hypertensive patients aged greater than 6 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults (see DOSAGE AND ADMINISTRATION). 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 ADMINISTRATION, Recommended Dose and Dosage Adjustment). Slow dose titration and careful monitoring are required in patients with severe hepatic impairment.

STORAGE AND STABILITY

Store at 15 – 30ºC. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pharma-AMLODIPINE is available as the following:

Oral Tablets

2.5 mg:	White to off white, diamond shaped, flat-faced, beveled edged uncoated tablets engraved with “A” on one side and plain other side.
5 mg:	White to off white, elongated octagonal shaped, flat-faced, beveled edged uncoated tablets engraved with “A” and “5” on either side of break line and plain on one side.
10 mg:	White to off white, elongated octagonal shaped, flat-faced, beveled edged uncoated tablets engraved with “A10” on one side and plain on one side.

Composition:

pharma-AMLODIPINE is available in 3 strengths, namely 2.5, 5 & 10 mg. Each tablet contains amlodipine besylate equivalent to 2.5 mg, 5 mg & 10 mg amlodipine per tablet.

The following inactive ingredients are common to all tablet strengths: magnesium stearate, microcrystalline cellulose, sodium starch glycolate and trisodium citrate.

Packaging

Available in:

2.5 mg - HDPE Bottles of 100's
5 mg - HDPE Bottles of 100's and 250’s
10 mg - HDPE Bottles of 100's and 250’s

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

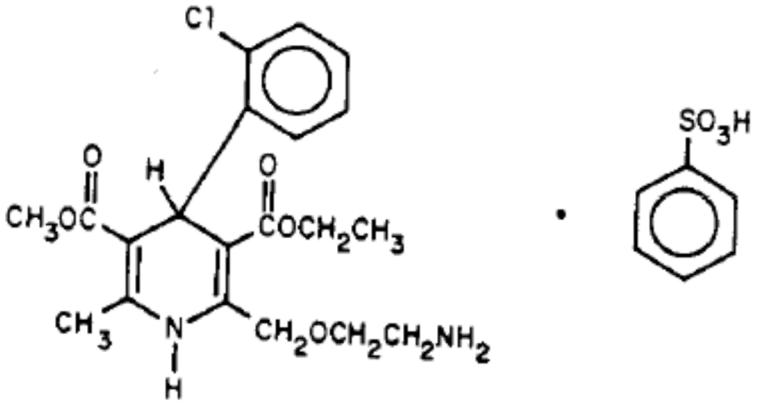
Proper name: Amlodipine Besylate

Chemical name: 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate.

Molecular formula: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$

Molecular Weight: 567.1 g/mol

Structural formula:



Physicochemical properties:

Description: Amlodipine besylate is a white crystalline substance, slightly soluble in water and sparingly soluble in ethanol.

Melting Point: 203ºC with decomposition.

pKa: 9.02 at 23.5ºC.

CLINICAL TRIALS

Comparative Bioavailability Studies

A single-dose, cross-over design comparative bioavailability study of pharma-AMLODIPINE 10 mg [Pharmascience Inc.] versus Norvasc® 10 mg tablets [Pfizer Canada Inc.] has been performed in 18 in healthy, adult, human male subjects under fasting conditions. A summary of the bioavailability data is tabulated below.

Amlodipine (1 x10 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter**	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_{0-72} (ng*h/mL)	264.327, 270.167(21.0%)	267.701, 270.816 (24.1%)	100.6	96.51 - 104.90
C_{max} (ng/mL)	6.856, 7.026 (22.0%)	6.756, 6.971 (23.1%)	101.5	96.47 - 106.74
T_{max}§ (h)	7.500 (5.000 -10.000)	7.000 (5.000 -12.000)		

*pharma-AMLODIPINE 10 mg (Pharmascience Inc.)

† Norvasc® 10 mg Tablets (Pfizer Canada Inc., Canada) was purchased in Canada

§ Expressed as the median (range) only

** Due to the design of the study, meaningful AUC_I and $T_{1/2}$ parameters could not be determined.

DETAILED PHARMACOLOGY

ANIMAL

a. Mechanism of Action Studies – *In Vitro*

Amlodipine inhibited both calcium-induced and potassium-depolarisation-induced contractions of rat aorta. The inhibitory effect was gradual. The potency of amlodipine was more than 10-fold greater against Ca^{2+} -responses than against K^+ -responses. Studies in both rat aorta and dog coronary artery indicated that amlodipine was a competitive antagonist. Radioligand binding experiments designed to characterize the interactions of amlodipine with calcium channel binding sites in bovine brain and in cardiac membranes from dog and rat showed that amlodipine interacts competitively and at high affinity with the dihydropyridine (DHP) recognition site.

Amlodipine has been demonstrated to block constriction of coronary arteries and arterioles in response to calcium, potassium, epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*.

Electrophysiological experiments conducted using isolated papillary muscles from guinea pig hearts confirmed that amlodipine was a highly selective calcium channel blocker which inhibited cardiac slow action potentials in a non-use-dependent manner and with no effect on the fast Na^+ -channel.

In Langendorff-perfused guinea pig hearts, amlodipine showed negative inotropic activity, the concentration producing a 50% inhibition of cardiac contraction being approximately 10 times greater (20.2 nM) than for a 50% inhibition of vascular muscle contraction (1.9 nM). The drug displayed modest negative chronotropic effect (approximately 20%) at a concentration of 50 nM, approximately twice that required for 50% inhibition of cardiac contraction in the same preparation. Using Langendorff-perfused rat hearts the concentration producing a 50% inhibition of cardiac contraction was 300 times greater than for inhibition of coronary artery contraction.

b. Cardiovascular Activity – *In Vivo*

In anesthetized dogs, amlodipine (i.v. 25-1600 mcg/kg) was a potent coronary and peripheral vasodilator; ED_{50} values were 103 and 212 mcg/kg for reductions of coronary and systemic vascular resistances respectively. The reductions in vascular resistance were associated with corresponding increases in cardiac output, coronary flow, heart rate and myocardial contractility. Amlodipine possessed slow onset of action, minimal effect on blood pressure, and a long duration of action. Amlodipine caused slight, transient negative inotropic responses only at the highest dose, in excess of that required to cause maximal vasodilatation. The drug did not adversely affect atrial ventricular conduction, as assessed by PR interval.

Oral administration of amlodipine (0.5 to 2.0 mg/kg) to conscious dogs produced dose-related reductions in systemic vascular resistance (max. of 78%) and reflexly-induced increases in heart rate cardiac output and myocardial contractility; maximum effects were achieved much later (3 to 5h) than after parenteral administration (5 to 30 min) which may

explain the dose- related modest blood pressure reductions (max. change of 25%) observed by the oral route.

c. Antihypertensive Efficacy -*In Vivo*

Amlodipine produced dose-related reductions in blood pressure of spontaneously hypertensive rats (SHR) after oral administration. The antihypertensive effect was maintained for at least 6h after each one of the 3 doses used (1, 3, and 10 mg/kg). In young SHR the development of hypertension was attenuated by 60% over a 12-week period when amlodipine was added to the diet to provide the dose of 8 mg/kg/day. In mature SHR receiving amlodipine for 8 weeks, a marked antihypertensive effect was evident by day 2 and attained a maximum by day 5. This effect was maintained for the remaining treatment period with no change in heart rate. In addition, treated animals showed a small, but statistically significant, reduction in ventricular weight and marked elevation in plasma renin activity.

In conscious renal-hypertensive dogs, oral administration of single doses of amlodipine (0.25, 0.5 and 1.0 mg/kg) produced dose-related reductions in blood pressures with maximum effects occurring at 5 h after dose. These responses were accompanied by dose-related increases in heart rate.

The slow onset and long-lasting antihypertensive effects of amlodipine were confirmed in conscious renal-hypertensive dogs in which blood pressure was recorded continuously for 24 h.

In conscious renal-hypertensive dogs, orally-administered amlodipine (0.025, 0.05 and 0.25 mg/kg/day) for 10-14 days produced progressive reductions in the daily, resting, pre-dose blood pressure which stabilized after 4 or 5 days. The minimum blood pressures achieved each day were approximately equivalent and tolerance did not develop. Heart rate was inconsistently affected.

d. General Pharmacology

In both normotensive (fluid-loaded) and spontaneously hypertensive rats (SHR) amlodipine produced diuresis and natriuresis. A diuretic effect was also observed in saline loaded conscious or anesthetized dogs treated with low intravenous doses (less than 0.4 mg/kg) of amlodipine; increases in potassium excretion were not significant. Also in the conscious rat amlodipine produced dose-related reduction of basal gastric acid secretion and a small but significant reduction in gastro-intestinal motility. Experiments in anesthetized dogs indicated that phenylephrine was an effective antidote to the hypotensive effect of a supra-maximal dose of amlodipine.

TOXICOLOGY

Acute Toxicity – Amlodipine (as maleate unless otherwise indicated)

			LD_{50}	Range of Lethal Doses(mg/kg)	
Species	**Sex**	**Route**	**base/mg/kg**	**No Deaths**	**All Dead**
Mice	M	p.o.	N.D.	10	40
	F	p.o.	N.D.	10	40
	M	i.v.	N.D.	2.5	10
	F	i.v.	N.D.	2.5	10
Rats	M	p.o.	150	2/10 at 100	400
	F	p.o.	140	2/10 at 100	250
	M	i.v.	N.D.	1	10
	F	i.v.	N.D.	1	10
Rats*	M	p.o.	393**		
	F	p.o.	686**		

* Sprague Dawley Rats from Shizouka Lab Animal Centre, Hamamatsu, Japan
** Besylate Salt
\+ Dogs from Interfauna, France
++ Dogs from Japan
N.D. Not Determined: The result did not permit calculations of LD_{50} values. Thus, range of lethal doses is given

The main clinical signs in the oral studies were somnolence, decreased spontaneous movement and for rats, salivation, dyspnea, ptosis, lacrimation, blanching, cyanosis, rough coat, abdominal distension, and eventually coma. After i.v. injection, the animals died rapidly showing only somnolence, tachypnea or ptosis.

Species	Route	Dose Base mg/kg/day	Animal per dose level	Duration	Findings
MAXIMUM TOLERATED DOSE (SINGLE)					
Dog	Oral (gavage)	4 8 16	2 M	Single Dose	At all dose levels: Vasodilation and increases in plasma aldosterone levels. At 4 mg/kg: Compensatory tachycardia. At 8 mg/kg: In 1 of 2 dogs vomiting, sedation, respiratory distress and diarrhea 48 hr post-dose; normal at day 5. Compensatory tachycardia. At 16 mg/kg: Moribund with hyperthermia within 24 hours; low blood pressure returned to normal over 2-6 days; transient raise in heart rate. Histological examination: showed congestion, edema and hemorrhage of the right atrial wall in the 2 dogs at 16 mg/kg. The hemorrhage in the right atrial wall corresponds to the right atrial lesions seen in long-term studies with amlodipine and other vasodilators (see long-term toxicity). One of 2 dogs at each dose showed fibrosis of the left ventricle in the subendocardial region and the posterior papillary muscle. The maximum tolerated dose was not determined.

Species	Route	Dose Base mg/kg/day	Animal per dose level	Duration	Findings
Dog (Japanese Study)	Oral	3.5 7	1 M 1 F	Single Dose	Mortality: 1 male dog at 7 mg/kg. Decreased spontaneous movement and flushing of palpebral conjunctiva and buccal cavity. At 7 mg/kg: 1 female vomiting; 1 male hypothermia, lying prone. Hematology/Clinical Chemistry: Increase in WBC and BUN at 10 and 5 mg/kg (males). The maximum tolerated dose was not determined.
SUBACUTE AND CHRONIC TOXICITY					
Mouse	Oral (diet)	0 2.5 5 10	10 M 10 F	2 Months	At 10 mg/kg/day: Mice died during week 2 of the study. At 5 mg/kg/day (males and females) and 2.5 mg/kg/day (males): Increase in water consumption. At 5 mg/kg/day – Pathology: Drug-related increases in heart and liver weights.
Rat (Japanese Study)	Oral (gavage)	0 4 16 32 64	12 M 12 F	1 Month	At 64 mg/kg/day: All rats died within 9 days. At 32 mg/kg/day: 12/24 rats died; decreased food consumption, growth inhibition, ptosis, decreased spontaneous movement. At 16 and 32 mg/kg/day: The pattern of results on heart weights, increased urinary volume, effect on electrolyte balance and the adrenals was similar to that of the 6 month study below; increase in BUN at 16 mg/kg (males) and at 32 mg/kg (males and females).
Rat (Japanese Study)	Oral (gavage)	0 2 7 21	16 M 16 F	3 Months followed by 1 Month drug withdrawal	21 mg/kg/day: Salivation, growth inhibition, increased BUN, increased urinary volume, effect on electrolyte balance and adrenals was similar to that of the 6-month study below. Also post-mortem dilation of small intestine without morphological lesions. At 7 mg/kg/day: Alterations in urinary electrolytes excretion. No drug related effects at the end of 1-month drug withdrawal phase.
Rat	Oral (gavage)	0 2.5 5 10	20 M 20 F	6 Months	At all dose levels: Renal effects: increased urinary volume and/or Na/K/Cl excretion, decreased plasma Na/K and/or Ca/Cl and increased urea; Post-mortem: Increase in heart weights. At 10 mg/kg/day: Renal effects: increased kidney weight. Histopathology: Thickening of zona glomerulosa at 5 and 10 mg/kg/day.
Rat (Japanese Study)	Oral (gavage)	1.4 7 18	30 M 30 F	12 Months (interim sacrifice 5/sex/group after 6 months)	Mortality: 3 rats (2 males and 1 female) at 18 mg/kg/day. At 18 mg/kg/day: Salivation, growth inhibition; Renal effects; increase in urinary volume with increased electrolytes excretion and decreased serum electrolytes; increase in BUN.

Species	Route	Dose Base mg/kg/day	Animal per dose level	Duration	Findings
					At 7 mg/kg/day: Growth inhibition (males); Renal effects: increases of urinary volume and electrolyte excretion. Post-mortem: Increases of adrenal weights (at 18 mg/kg), increases of relative heart weight (18 and 7 mg/kg), dilated small intestines without morphological change (18 mg/kg). Histopathology – Main Finding: Enlargement of the zona glomerulosa of the adrenals (18 and 7 mg/kg).
Dog	Oral (gavage)	0.5 to 4	2 M 2 F	10 days Supplementary Dose Escalation Study (0.5 mg/kg/day)	At 4 mg/kg: Death of all (4/4) dogs preceded in 3 dogs by low systolic blood pressure, bradycardia, disturbances of heart rhythm and conduction. Clinical signs included pale skin, hypothermia and prostration. Histopathology: Showed foci of myocyte necrosis and sarcoplasmic vacuolation in the left ventricle, papillary muscle and left and right atria. Congestion and/or edema in several organs (i.e. gastrointestinal tract/gall bladder wall and surrounding tissues as well as the connective tissue surrounding both kidneys).
Dog	Oral	0 0.25 0.5 1	3 M 3 F	6 Months	At all dose levels: Increase in urinary volume and urinary excretion of electrolytes (not dose-related). Reduction in blood pressure and increases in heart rate. At 1 mg/kg/day – Pathology: Increase in relative heart weights in 4/6 dogs, inflammatory lesion of the right atrial wall was seen which was considered to be consequence of excessive hemodynamic changes.
Dog	Oral	0 0.125 0.25 0.5	4 M 4 F	12 Months	At 0.5 mg/kg/day: Reduction in blood pressure and increases in heart rate; increase in urinary volume and urinary excretion of electrolytes (females). At 0.5 mg/kg/day – pathology: Showed inflammatory lesions of the right atrial wall in 1/8 dogs, similar to that of the 6-month study above, and diffuse gingival hyperplasia.

MUTAGENICITY

Study	Test Organism	Dose	Route	Major Findings
Ames Test (modified) Quantitative Plate Assay (QAP) and Metabolic Activation (MA) with Hepatic Microsomes	Salmonella typhimurium: Strains TA 1535, TA 1537, TA 98 and TA 100	10-0.02 mg/plate (QAP) 0.2-0.0005 mg/plate (MA)	*In vitro*	No evidence of mutation frequency.
In-vivo Cytogenetic Tests	Mouse bone marrow	20 mg/kg single dose 10 mg/kg/day for 5 days	*In vivo* p.o. s.c.	No indication of chromosome breakage or mutagenicity observed.
In-vitro Cytogenetic Tests with or without metabolic activation [rat liver microsomal enzymes (S-9)]	Human lymphocytes	Without metabolic activation: 0.01 to 1000 mcg/mL of culture medium. With metabolic activation: 1.0 to 25 mcg/mL of culture medium.	*In vitro*	Non-activation: No evidence of induced chromosome breakage observed at levels of 1.0 mcg/mL and below. At levels higher than 1.0 mcg/mL, compound produced mitotic inhibition. Activation: No drug induced clastogenic activity observed at levels up to 10 mcg/mL. Higher levels produced mitotic inhibition.
Quantitative Plate Assay (QAP) of Mouse Urine	Salmonella typhimurium Strains: TA 1535, TA 1537, TA 98 and TA 100	0, 1, 10 and 20 mg/kg	*In vivo* p.o.	No incidence of an excreted mutagen.
L 5178Y/TK +/- Gene Mutation Assay with and without liver S-9 fraction	Mouse lymphoma cells	1.2-38 mcg/mL	*In vitro*	No evidence of gene mutational activity.

CARCINOGENICITY

There was no evidence of a carcinogenic effect when amlodipine was administered in the diet for up to 24 months to rats up to 2.5 mg/kg/day. Amlodipine was also administered for up to 24 months of dietary administration to mice at doses up to 2.5 mg/kg/day and no evidence of carcinogenicity was observed.

REPRODUCTION AND TERATOLOGY

Species	Route	Dose base/mg/kg/ day	Animal per Dose Level	Duration	Findings
Fertility					
Rat (SD) (Japanese Study)	Oral (gavage)	0 1.4 7 18	24 M + 24 F	Males 71 days prior to and during mating. Females 14 days prior to and during mating and up to 7 days of gestation.	At 18 mg/kg: Impairment of body weight gain (females). There were no effects of the drug on copulation or pregnancy rates, nor any evidence of embryotoxicity or teratogenicity.
Teratology					
Rat (Charles River CD/SD)	Oral (gavage)	0 2 5 10	20 F	Days 6-15 post insemination. Hysterectomies on day 20 of gestation.	No effects were observed.
Rat (SD) Japanese Study	Oral (gavage)	0 3 7 18	34 F	Days 7-17 post- insemination. $^{2/3}$ of dams sacrificed on day 21 of gestation. F_1 generation followed.	No effects were observed except in the dams. At 18 mg/kg: Reduction in food intake and body weight gain.
Rabbit (Japanese White) Japanese Study	Oral	0 3 7 18	18 or 19 F	Day 6 to day 18 of gestation.	At 18 and 7 mg/kg: Decrease in maternal body weight (18 mg/kg) decrease in food consumption (18 and 7 mg/kg). No evidence of drug induced fetotoxicity or teratogenicity.
Peri- and Post-Natal					
Rat (SD) Japanese Study	Oral (gavage)	0 1.4 2.8 7.0	25 F	Day 17 of gestation to day 21 post-partum	As in the combined Fertility/Perinatal Study above; at the high dose level (7.0 mg/kg/day) adverse effects were observed on parturition and number of viable pups at birth and day 4 post-partum.

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 8 times greater than the maximum recommended dosage for humans.

Impairment of fertility

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses ≤ 10 mg amlodipine/kg/day (about 8 times the maximum recommended human dose of 10 mg/day on a mg/m2 basis, for a 50 kg human).

In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

REFERENCES

1. Abernethy DR, Gutkowska J, Lambert MD. Amlodipine in elderly hypertensive patients: pharmacokinetics and pharmacodynamics. J Cardiovasc Pharmacol 1988; 12(Suppl 7): S67-71.

2. Bernink PJLM, de Weerd P, ten Cate FJ, Remme WJ, Barth J, Enthoven R, Haagen FDM, Holwerda NJ, Klomps HC, and Coinvestigators. An 8-week double-blind study of amlodipine and diltiazem in patients with stable exertional angina pectoris. J Cardiovasc Pharmacol 1991; 17(Suppl 1): S53-6.

3. Burris JF, Ames RP, Applegate WB, Ram CVS, Davidov ME, Mroczek WJ. Double-blind comparison of amlodipine and hydrochlorothiazide in patients with mild to moderate hypertension. J Cardiovasc Pharmacol 1988;12(Suppl 7):S98-102.

4. Cappuccio FP, Markandu ND, Sagnella GA, Singer DRJ, Buckley MG, Miller MA, MacGregor GA. Effects of amlodipine on urinary sodium excretion, renin-angiotensin-aldosterone system, atrial natriuretic peptide and blood pressure in essential hypertension. J Hum Hypertens 1991;5:115-19.

5. Flynn JT. A Randomized, Placebo-Controlled Trial of Amlodipine in Children with Hypertension. J Pediat 2004; Vol 145/3 pp:353-359.

6. Frishman WH, Brobyn R, Brown RD, Johnson BF, Reeves RL, Wombolt DG. A randomized placebo-controlled comparison of amlodipine and atenolol in mild to moderate systemic hypertension. J Cardiovasc Pharmacol 1988;12 (Suppl 7): S103-6.

7. Gandhi, Sonja, et al. Calcium-Channel Blocker-Clarithromycin Drug Interactions and Acute Kidney Injury. JAMA 310.23 (2013): 2544-2553

8. Glasser SP, Chrysant SG, Graves J, Rofman B, Koehn DK. Safety and efficacy of amlodipine added to hydrochlorothiazide therapy in essential hypertension. Am J Hypertens 1989;2:154-7.

9. Glasser SP, West TW. Clinical safety and efficacy of once-a-day amlodipine for chronic stable angina pectoris. Am J Cardiol 1988;62:518-22.

10. Hosie J, Bremner AD, Fell PJ, James IGV, Saul PA, Taylor SH. Comparison of early side effects with amlodipine and nifedipine retard in hypertension. Cardiology 1992;80(Suppl 1):54-9.

11. Klein W, Mitrovic V, Neuss H, Schlepper M, Cocco G, Prager G, Fitscha P, Meisner W.
    a. A 6-week double-blind comparison of amlodipine and placebo in patients with stable exertional angina pectoris receiving concomitant β-blocker therapy. J Cardiovasc Pharmacol 1991; 17(Suppl 1):S50-2.

12. Lopez LM, Thorman AD, Mehta JL. Effects of amlodipine on blood pressure, heart rate, catecholamines, lipids and responses to adrenergic stimulus. Am J Cardiol 1990;66:1269-71.

13. Lorimer AR, Smedsrud T, Walker P, Tyler HM. Comparison of amlodipine and verapamil in the treatment of mild to moderate hypertension. J Cardiovasc Pharmacol 1988:12(Suppl 7):S89-93.

14. Lund-Johansen P, Omvik P, White W, Digranes O, Helland B, Jordal O, Stray T. Long-term haemodynamic effects of amlodipine at rest and during exercise in essential hypertension. J Hypertens 1990;8(12):1129-36.

15. Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. Clin Pharmacokinet b. 1992;22(1):22-31.

16. Murdoch D, Heel RC. Amlodipine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. Drugs 1991;41 (3):478-505.

17. Taylor SH. Amlodipine in post-infarction angina. Cardiology 1992;80(Suppl 1):26-30.

18. Taylor SH, Lee P, Jackson N, Cocco G. A double-blind placebo-controlled, parallel dose- response study of amlodipine in stable exertional angina pectoris. J Cardiovasc Pharmacol 1991; 17 (Suppl 1):S46-9.

19. Toupance O, Lavaud S, Canivet E, Bernaud C, Hotton JM, Chanard J. Antihypertensive effect of amlodipine and lack of interference with cyclosporine metabolism in renal transplant recipients. Hypertension 1994;24(3):297-300.

20. Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. Arch Intern Med 1991;151:1413-23.

21. Varonne J, Investigators of Study AML-NY-86-002. The efficacy and safety of amlodipine in the treatment of mild and moderate essential hypertension in general practice. J Cardiovasc Pharmacol 1991; 17(Suppl 1):S30-3.

22. Vetrovec G, Dailey S Kay GN, Epstein A, Plumb V. Hemodynamic and electrophysiologic effects of amlodipine, a new long-acting calcium antagonist: preliminary observations. Am Heart J 1989; 118(5Pt2):1104-5.

23. Product Monograph for Pr NORVASC® (Upjohn Canada ULC); Date of Revision: May 27, 2020. Control # 236351.

PART III: CONSUMER INFORMATION

[Pr] pharma-AMLODIPINE

Amlodipine Besylate Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when pharma-AMLODIPINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pharma-AMLODIPINE. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

pharma-AMLODIPINE has been prescribed to you for:

- The treatment of high blood pressure (hypertension), or
- The management of a type of chest pain called angina.

pharma-AMLODIPINE can be used by itself or with other medicines to treat these conditions.

What it does:

pharma-AMLODIPINE is a type of medicine known as a calcium channel blocker (CCB).

pharma-AMLODIPINE relaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure.

pharma-AMLODIPINE controls chest pain by improving the supply of blood and oxygen to the heart and by reducing its workload.

When it should not be used:

Do not use pharma-AMLODIPINE if you:

- Are allergic to amlodipine (the active ingredient in pharma-AMLODIPINE), or to the inactive ingredients listed under "**What the nonmedicinal ingredients are**" below.
- Have ever had an allergic reaction to a similar type of drug.
- Have very low blood pressure (less than 90 mmHg systolic).
- Have been diagnosed with aortic stenosis (narrowing of the aortic heart valve).
- Have been diagnosed with unstable heart failure after a heart attack.
- Experience shock including cardiogenic shock.
- Are breast-feeding. Do NOT breast-feed while taking pharma-AMLODIPINE.

What the medicinal ingredient is:

Amlodipine besylate

What the nonmedicinal ingredients are:

Magnesium stearate, microcrystalline cellulose, sodium starch glycolate and trisodium citrate.

What dosage forms it comes in:

Tablets 2.5 mg, 5 mg and 10 mg amlodipine (as amlodipine besylate).

WARNINGS AND PRECAUTIONS

BEFORE you use pharma-AMLODIPINE talk to your doctor, nurse or pharmacist if you:

- Ever had heart or blood vessel diseases.
- Have aortic stenosis (narrowing of a valve of your heart).
- Have liver or kidney problems.
- Are pregnant, or plan to become pregnant. pharma-AMLODIPINE should not be used during pregnancy unless your doctor tells you otherwise.
- Are older than 65 years.

pharma-AMLODIPINE may occasionally cause low blood pressure (hypotension). Your blood pressure should be carefully monitored, especially if you have had a stroke or take other drugs to lower your blood pressure.

If you take pharma-AMLODIPINE together with a drug known as beta-blockers (*e.g.* acebutolol, atenolol, metoprolol, nadolol), do not suddenly stop using the beta-blocker. If your doctor advises you to discontinue use of the beta-blocker, your dose should be decreased slowly, as recommended by your doctor, before stopping it completely.

pharma-AMLODIPINE is not recommended for use in children less than 6 years of age.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines. Also, mention if you drink alcoholic beverages.

Drug-Drug interaction:

Drugs that may interact with pharma-AMLODIPINE include:

- Cyclosporin
- Clarithromycin, Erythromycin (antibiotics)
- Diltiazem
- Azole antifungals (e.g. ketoconazole, itraconazole)
- HIV protease inhibitors (e.g. ritonavir)
- Beta-blockers
- Sildenafil
- Statin drugs used to treat high cholesterol (e.g. Simvastatin, Atorvastatin)
- Tacrolimus (an anti-rejection drug)
- Sirolimus, temsirolimus, everolimus
- Dantrolene

Drug-Herb interaction:

- St. John's Wort

Drug-Food interaction:

Do not eat grapefruit or drink grapefruit juice while on pharma-AMLODIPINE.

PROPER USE OF THIS MEDICATION

Take pharma-AMLODIPINE exactly as prescribed by your doctor, nurse or pharmacist. 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 stop taking your medication without having first informed your doctor.

Usual dose:

For both high blood pressure and chest pain, the recommended initial dose of pharma-AMLODIPINE is 5 mg once daily. If necessary, your doctor may increase your dose to a maximum dose of 10 mg once daily.

Use in Patients with liver disease:
The starting dose is 2.5 mg once daily and can be gradually increased by your doctor.

Use in Children (6-17 years old):
The recommended dose is 2.5 mg to 5 mg once daily.

Overdose:

If you think you have taken too much pharma-AMLODIPINE contact your healthcare professional, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

One or more of the following signs may occur in an overdose: Low blood pressure and rapid heartbeat.

Missed Dose:
If you miss a dose, take it as soon as you remember. If it has been more than 12 hours since you missed your last dose, skip the missed dose and continue with the next dose at your regular time. Do not take double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects include:

- Headaches
- Tiredness, extreme sleepiness
- Stomach pain, nausea
- Dizziness

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / Effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	**Flushing:** Hot or warm feeling in your face	✓		
Common	**Edema:** Swelling of your legs or ankles	✓		
Uncommon	**Arrhythmia:** Rapid, slow or irregular heartbeat		✓	
Uncommon	**Increased frequency, severity, duration of angina:** pressing or squeezing pain in your chest		✓	
	Heart Attack: Pain, fullness and/or squeezing of the chest, jaw pain and/or arm pain, shortness of breath			✓
	Liver Disorder: Yellowing of the skin or eye, dark urine, abdominal pain nausea, vomiting, loss of appetite		✓	
	Allergic Reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty breathing or swallowing			✓
	Low Blood Pressure: Dizziness, fainting, lightheadedness may occur when you go from lying or sitting to standing up	✓		
Unknown	**Extrapyramidal symptoms:** Muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.			✓

This is not a complete list of side effects. For any unexpected effects while taking pharma-AMLODIPINE, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Keep pharma-AMLODIPINE out of the reach and sight of children. Store pharma-AMLODIPINE at room temperature (between 15-30ºC). Protect pharma-AMLODIPINE from light.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about pharma-AMLODIPINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by calling the sponsor Pharmascience Inc. at: 1-888-550-6060.

This leaflet was prepared by:

Pharmascience Inc.
Montréal, Québec
H4P 2T4

www.pharmascience.com

Last revised: January 5, 2021