

APO-AMLODIPINE 2.5 mg, 5 mg, 10 mg TABLETS**NAME OF THE MEDICINE**

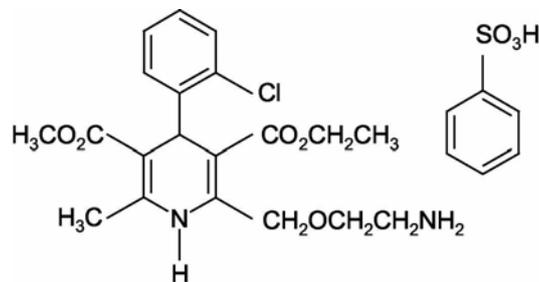
Amlodipine besylate.

DESCRIPTION

Amlodipine besylate is a dihydropyridine derivative.

Chemical Name: 3-ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate.

Structural Formula:



Molecular Weight: 567.1 (free base 408.9).

Amlodipine besylate is a white crystalline powder and is slightly soluble in water and sparingly soluble in ethanol.

In addition to amlodipine besylate, each tablet contains the following inactive ingredients: lactose, microcrystalline cellulose, maize starch and magnesium stearate.

ACTIONS

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound ($pK_a=8.6$), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces the total ischaemic burden by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. Amlodipine has been shown to block constriction in main coronary arteries and coronary arterioles, induced by calcium, potassium, adrenaline, serotonin and thromboxane A2 analogue both in normal and in ischaemic regions.

Haemodynamics

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreased arterial blood pressure and increased heart rate in haemodynamic studies of patients with chronic stable angina, chronic administration of oral amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.

The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+ 1/2 mmHg).

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine 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 haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when coadministered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

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 or proteinuria.

CLINICAL TRIALS

Studies in Patients with Congestive Heart Failure

Amlodipine has been compared to placebo in four 8-12 weeks studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. Although efficacy in regard to the primary and secondary endpoints was not demonstrated, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure.

Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo: the cardiac morbid events represented about 25% of the endpoints in the study.

In this study amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

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 minute 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 alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Effects in Hypertension

In patients with hypertension once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval post dose. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. The blood pressure effect is maintained over the 24 hour dosing interval, with little difference in peak and trough effect. Tolerance has not been demonstrated in patients studied for up to 1 year. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure.

Effects in Chronic Stable Angina

In patients with angina, once daily administration of amlodipine increases total exercise time to angina onset and total work time to 1 mm ST segment depression and decreases both angina attack frequency and nitroglycerine tablet consumption. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Other

In clinical trials amlodipine has shown no harmful effect on lipid levels. Dihydropyridine calcium channel blockers have not been associated with any adverse metabolic effects and are suitable for use in patients with asthma, diabetes and gout.

PHARMACOKINETICS AND METABOLISM

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours postdose. This may reflect significant initial uptake by the liver, followed by a phase of redistribution. This interval is shorter (2-8 hours) in patients with hepatic insufficiency. Absolute bioavailability has been estimated to be between 64 and 90%.

The bioavailability of amlodipine is not altered by the presence of food. The volume of distribution is approximately 20 L/kg. The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing.

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%.

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

INDICATIONS

1. Hypertension

Apo-Amlodipine is indicated for the first line treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent may benefit from the addition of Apo-Amlodipine, which has been used in combination with a thiazide diuretic, beta adrenoceptor blocking agent or an angiotensin-converting enzyme inhibitor.

2. Angina

Apo-Amlodipine is indicated for the first line treatment of chronic stable angina. Apo-Amlodipine may be used alone, as monotherapy or in combination with other antianginal drugs.

CONTRAINDICATIONS

Apo-Amlodipine is contraindicated in patients with a known sensitivity to amlodipine, dihydropyridines, or any of the inactive ingredients.

PRECAUTIONS

Increased Angina

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

Outflow Obstruction (Aortic Stenosis)

Apo-Amlodipine should be used with caution in the presence of a fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Congestive Heart Failure

In general, calcium channel blockers should be used with caution in patients with heart failure. amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalisation for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal

Amlodipine is not a beta-blocker and therefore provides no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

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 doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur. Amlodipine 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).

Use in Renal Failure

Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses.

Amlodipine is not dialysable.

Carcinogenicity

The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

Use During Pregnancy – Category C

Category C Definition – Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

Safety of amlodipine in human pregnancy or lactation has not been established. In animal studies, amlodipine did not affect fertility in rats at oral doses up to 18 mg/kg (base) and had no teratogenic effects in rats (18 mg/kg) or rabbits (10 mg/kg). Amlodipine (10 mg/kg as besylate salt, 7 mg/kg base), administered orally to rats at or near parturition induced a prolongation of gestation time, an increase in the number of stillbirths and a decreased postnatal survival.

Use During Lactation

It is not known whether amlodipine is excreted in human milk. In the absence of this information, breast-feeding should be discontinued during treatment with amlodipine.

Use in the Elderly

In elderly patients (≥ 65 years) clearance of amlodipine is decreased with a resulting increase in AUC. 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 oedema, muscle cramps and dizziness. Amlodipine should be used cautiously in elderly patients.

Peripheral Oedema

Mild to moderate peripheral oedema was the most common adverse event in the clinical trials (see **ADVERSE EFFECTS**). The incidence of peripheral oedema 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 oedema from the effects of increasing left ventricular dysfunction.

Use in Children

Safety and effectiveness have not been established in children.

INTERACTIONS WITH OTHER MEDICINES

Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycaemic drugs.

Special studies have indicated that the co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, and that coadministration of cimetidine did not alter the pharmacokinetics of amlodipine; and that coadministration with warfarin did not change the warfarin prothrombin response time.

In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indomethacin).

Grapefruit Juice

Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers.

In a study in 20 healthy volunteers, co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg had no significant effect on the pharmacokinetics of amlodipine.

Aluminium / Magnesium (Antacid)

Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil

A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin

Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Ethanol (Alcohol)

Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Cyclosporin

The pharmacokinetics of cyclosporin were not altered when cyclosporin was co-administered with amlodipine in renal transplant patients. The patients were not taking corticosteroids.

ADVERSE EFFECTS

Amlodipine has been evaluated for safety in more than 11000 patients in clinical trials worldwide.

In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity.

In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%).

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen or creatinine or liver function tests.

The most common side effects are headache and oedema.

The incidence (%) of side effects which occurred in a dose related manner are as follows:

	2.5 mg	5.0 mg	10.0 mg	Placebo
Adverse Event	N = 275	N = 296	N = 268	N = 520
Oedema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Adverse Event	Placebo Controlled Studies	
	Amlodipine % (N = 1730)	Placebo % (N = 1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

The following events occurred in $\leq 1\%$ but $> 0.1\%$ of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular

Hypotension, peripheral ischaemia, syncope, tachycardia, postural dizziness, postural hypotension, angioedema.

Central and Peripheral Nervous System

Hypoesthesia, paresthesia, tremor, vertigo, peripheral neuropathy.

Gastrointestinal

Anorexia, constipation, dyspepsia, dysphagia, diarrhoea, flatulence, vomiting, altered bowel habits, pancreatitis, gingival hyperplasia.

General

Allergic reactions, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain.

Musculo-Skeletal System

Arthralgia, arthrosis, muscle cramps, myalgia.

Psychiatric

Sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalisation, mood changes.

Respiratory System

Dyspnoea, epistaxis.

Skin and Appendages

Alopecia, pruritus, rash, rash erythematous, rash maculopapular, vasculitis.

Special Senses

Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System

Micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System

Dry mouth, sweating increased.

Metabolic and Nutritional

Thirst, hyperglycaemia.

Haemopoietic

Purpura, leucopenia, thrombocytopenia.

Endocrine

Gynaecomastia.

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, pulse irregularity, extrasystoles, skin discolouration, urticaria, skin dryness, dermatitis, erythema multiforme, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, xerophthalmia and weight decrease.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

There have been infrequent, post marketing reports of hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus and abnormal lipid profiles.

DOSAGE AND ADMINISTRATION

For hypertension or angina the usual initial dose is 2.5 to 5 mg once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

Small, fragile or elderly individuals, or patients with hepatic insufficiency should be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently. See **ADVERSE EFFECTS** section for information related to dosage and side effects.

Co-Administration with Other Antihypertensive and/or Antianginal Drugs

Amlodipine has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta-blockers, long-acting nitrates and angiotensin-converting enzyme inhibitors.

OVERDOSAGE

Available data suggest that overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia.

Dysrhythmias may occur following overdose with any calcium antagonists.

Hypotension and bradycardia are usually seen within 1 to 5 hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to 7 days. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalised; another (120 mg) was hospitalised, underwent gastric lavage and remained normotensive; a third one (105 mg) was hospitalised and had hypotension (90/50 mmHg) which normalised following plasma expansion.

Death resulted from a mixed overdose of 140 mg and 10 mefenamic acid capsules in a 15-year old girl, and from a mixed overdose of amlodipine 70 mg and an unknown quantity of oxazepam in a 63-year old woman. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium may help to reverse the effects of calcium entry blockade.

Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecac-emesis is not recommended since haemodynamic instability and CNS depression may rapidly develop*.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

*** Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.**

PRESENTATION AND STORAGE CONDITIONS

2.5 mg: white to off-white, round unscored uncoated imprinted “APO” on one side and “AML” over “2.5” on the other side.

Blister pack of 30 tablets (not marketed).

Bottle of 30 tablets (not marketed).

5 mg: white to off-white, round flat-faced beveled-edge scored tablets, engraved “AML” over score “5” on one side and “APO” on the other side.

Blister pack of 30 tablets.

Bottle of 30 tablets (not marketed).

10 mg: white to off-white, round unscored uncoated tablets, engraved “APO” on one side and “AML” over “10” on the other side.

Blister pack of 30 tablets.

Bottle of 30 tablets (not marketed).

Storage

Store below 25°C. Store in the original package.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
ABN 52 096 916 418
66 Waterloo Road
North Ryde NSW 2113
Australia

Apotex Pty Ltd is the licensee of the registered trade marks AX logo, APO and APOTEX from the registered proprietor, Apotex Inc.

POISON SCHEDULE OF THE MEDICINE

Schedule 4: Prescription Only Medicine.

Date of TGA approval : 6 December 2007